WORLD INTELLECTUAL PROPERTY ORGANIZATION International Bureau



INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT) (51) International Patent Classification 6: WO 96/40679 (11) International Publication Number: C07D 401/06, A61K 31/44 A1 (43) International Publication Date: 19 December 1996 (19.12.96) Foxcroft Lane, Phoenixville, PA 19460 (US). SPADA, Al-(21) International Application Number: PCT/US96/09816 fred, P. [US/US]; 473 Painter Way, Lansdale, PA 19446 (US). CHOI-SLEDESKI, Yong, Mi [US/US]; 5 Dana Drive, (22) International Filing Date: 7 June 1996 (07.06.96) Collegeville, PA 19426 (US). (74) Agents: PARKER, Raymond, S. et al.; Rhône-Poulenc Rorer (30) Priority Data: Pharmaceuticals Inc., Mail Drop # 3C43, P.O. Box 5093, 08/481,024 7 June 1995 (07.06.95) US Collegeville, PA 19426-0997 (US). (60) Parent Application or Grant (63) Related by Continuation (81) Designated States: AL, AM, AT, AU, AZ, BB, BG, BR, BY, 08/481,024 (CIP) US CA, CH, CN, CZ, DE, DK, EE, ES, FI, GB, GE, HU, IS, Filed on 7 June 1995 (07.06.95) JP, KE, KG, KP, KR, KZ, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, TJ, TM, TR, TT, UA, UG, US, UZ, VN, (71) Applicant (for all designated States except US): RHÔNE-POULENC RORER PHARMACEUTICALS INC. [US/US]; ARIPO patent (KE, LS, MW, SD, SZ, UG), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent Legal-Patents, Mail Drop #3C43, P.O. Box 5093, Col-(AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, legeville, PA 19426-0997 (US). GA, GN, ML, MR, NE, SN, TD, TG). (72) Inventors; and (75) Inventors/Applicants (for US only): EWING, William, R. [US/US]; 805 Graystone Lane, Downingtown, PA 19335 Published (US). BECKER, Michael, R. [US/US]; 62 Church Road, With international search report. Norristown, PA 19401 (US). PAULS, Henry, W. [CA/US]; 3770 Worthington Circle, Collegeville, PA 19426 (US). CH-ENEY, Daniel, L. [US/US]; 836 Locust Street, Collegeville, PA 19426 (US). MASON, Jonathan, Stephen [GB/US]; 8 (54) Title: SUBSTTTUTED (SULFINIC ACID, SULFONIC ACID, SULFONYLAMINO SULFINYLAMINO) [(AMINOIMINOMETHYL)PHENYLALKYL]-AZAHETEROCYCLYLAMIDE COMPOUNDS

(57) Abstract

The compounds of formula (I) exhibit useful pharmacological activity and accordingly are incorporated into pharmaceutical compositions and used in the treatment of patients suffering from certain medical disorders. More especially, they are inhibitors of the activity of Factor Xa. The present invention is directed to compounds of formula (I), compositions containing compounds of formula (I) and their use, which are for treating a patient suffering from, or subject to, physiological condition which can be ameliorated by the administration of an inhibitor of the activity of Factor Xa. (1) I will be a subject to the administration of an inhibitor of the activity of Factor Xa.

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អស្នររយៈក្រោយ គឺ ស្រី សម្រេច (Color) The plant right is the property of the purposes of the purpose applications under the PCT. AM Armenia GB United Kingdom MW Malawi AT Austria GR Georgia MX Mexico AU Australia GN Guinea NE Niger BB Barbados GR Greece NL Netherlands Norway ΒE Belgium HIII Hungary NO RF Burkina Faso IE Ircland N7. New Zealand BG Bulgaria IT Italy Poland PL BJ Benin JP Japan PT **Portugal** BR Brazil KE Kenya RO Romania BY Belarus KG Kyrgystan RU Russian Pederation CA Canada KP Democratic People's Republic Sudan CF Central African Republic of Korea SE Sweden Republic of Korea CG Congo Singapore CH Switzerland ΚZ Kazakhstan SI Slovenia CI Côte d'Iveire Liechtenstein Slovakia LI CM Cameroon Sri Lanka Sencral CN China LR Liberia Swaziland CS Czechoslovakia Lithuania CZ LU Luxembourg Czech Republic Togo DE LV Germany Latvia Tajikistan DK MC Trinidad and Tobago Denmark Monaco EE Estonia MD Republic of Moldova Ukraine Madagascar ES MG Spain Uganda FI Finland ML Mali United States of America Prance MN Mongolia Uzbekistan Gabon MR Mauritania Viet Nam

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SUBSTITUTED (SULFINIC ACID, SULFONIC ACID, SULFONYLAMINO OR SULFINYLAMINO) No. 1 A 19 Y 19 20 N-[(AMINOIMINOMETHYL)PHENYLALKYL]- 1 10 AZAHETEROCYCLYLAMIDE COMPOUNDS

This application is a continuation-in-part of U.S. patent application Serial No. 08/481,024, filed June 7, 1995, to get the activities as on a special with the strain of the plant of the property throntoness and a second special parts and the plant of the property of the plant of the property of the plant of th

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The compounds of formula I exhibit useful pharmacological activity and accordingly are incorporated into pharmaceutical compositions and used in the treatment of patients suffering from certain medical disorders. More especially, 20 they are Factor Xa inhibitors. The present invention is directed to compounds of formula I, compositions containing compounds of formula I, and their use. which are for treating a patient suffering from, or subject to, conditions which can be ameliorated by the administration of an inhibitor of Factor Xana

25 Factor Xa is the penultimate enzyme in the coagulation cascade. Both free factor Xa and factor Xa assembled in the prothrombinase complex (Factor Xa, Factor Va, calcium and phospholipid) are inhibited by compounds of oformula la Factor Xa inhibition is obtained by direct complex formation between the inhibitor and the enzyme and is therefore independent of the plasma co-30 factor antithrombin III. Effective factor Xa inhibition is achieved by administering the compounds either by oral administration, continuous intravenous infusion, bolus intravenous administration or any other parenteral rouse such that it achieves the desired effect of preventing the factor Xa induced formation of thrombin from prothrombin.

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Anticoagulant therapy is indicated for the treatment and prophylaxis of a variety of thrombotic conditions of both the venous and arterial vasculature. In

the arterial system, abnormal thrombus formation is primarily associated with arteries of the coronary, cerebral and peripheral vasculature. The diseases associated with thrombotic occlusion of these vessels principally include acute myocardial infarction (AMI), unstable angina, thromboembolism, acute vessel closure associated with thrombolytic therapy and percutaneous transluminal 5 coronary angioplasty (PTCA), transient ischemic attacks, stroke, intermittent claudication and bypass grafting of the coronary (CABG) or peripheral arteries. Chronic anticoagulant therapy may also be beneficial in preventing the vessel luminal narrowing (restenosis) that often occurs following PTCA and CABG, and in the maintenance of vascular access patency in long-term hemodialysis 10 patients. With respect to the venous vasculature, pathologic thrombus to formation frequently occurs in the veins of the lower extremities following abdominal, knee and hip surgery (deep vein thrombosis, DVT). DVT fürther predisposes the patient to a higher risk of pulmonary thromboembolism. A systemic, disseminated intravascular coagulopathy: (DIC) commonly occurs in 15 both vascular systems during septic shock, certain viral infections and cancer. This condition is characterized by a rapid consumption of coaquiation factors and their plasma inhibitors resulting in the formation of life-threatening wastand throughout the microvasculature of several organ systems. The 20 Dundications discussed above include some, but not all, of the possible clinical situations where anticoagulant therapy is warranted. Those experienced in this field are well aware of the circumstances requiring either acute or chronic prophylactic anticoagulant therapy. Its in the end you be smalled as the prophylactic anticoagulant therapy.

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$$X_1$$
 X_1
 X_2
 X_2
 X_3
 X_4
 X_4
 X_5
 X_2
 X_2
 X_5
 X_6
 X_6
 X_6



is phenyl or monocyclic heteroaryl;

R is hydrogen, optionally substituted alkyl, optionally substituted aralkyl, optionally substituted heteroaralkyl or hydroxyalkyl;

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 R_1 is hydrogen, $R_3S(O)_p$ - or $R_3R_4NS(O)_p$ -;

" Altinos in the

- 10 R_2 is hydrogen, or when X_5 and X_5 taken together are =NR5, then R_2 is hydrogen, optionally substituted lower alkyl, optionally substituted aralkyl or optionally substituted heteroaralkyl;
- R₃ is optionally substituted alkyl, optionally substituted cycloalkyl, optionally substituted aryl, optionally substituted heterocyclyl, optionally substituted aralkyl, optionally substituted heteroaralkyl, optionally substituted aralkenyl or optionally substituted heteroaralkenyl, or R and R₃ taken together form a 5 to 7 membered ring; and the Sharehalle.
- 20 R₄ is optionally substituted alkyl, optionally substituted cycloalkyl or optionally substituted arallyl substituted heteroaryl, optionally substituted arallyl or optionally substituted heteroaralkyl, or R₃ and R₄ taken together with the nitrogen to which R₃ and R₄ are attached form an optionally substituted 4 to 7 membered heterocyclyl;

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 X_1 and X_1 are independently selected from hydrogen, optionally substituted alkyl, optionally substituted aryl, optionally substituted aralkyl, optionally

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m is 0, 1, 2 or 3;

substituted heteroaryl, optionally substituted heteroaralkyl or hydroxyalkyl, or X_1 and X_2 taken together form oxo;

X₂ and X₂ are hydrogen, or taken together form oxo;

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 X_3 is hydrogen, hydroxy, optionally substituted alkyl, optionally substituted aryl, optionally substituted heteroaryl, optionally substituted aralkyl or optionally substituted heteroaralkyl, or X_3 and one of X_1 and X_2 taken together form a 4 to 7 membered ring;

X₄ is hydrogen, optionally substituted alkyl, optionally substituted aralkyl, or hydroxyalkyl;

Prisonal of the property of the state of the

 X_s and X_s , are hydrogen or taken together are =NR_s;

15 γετα bets fiedus γθεποίτηο έγετη δε πθετάνε γθεποίται ευερφένε εί Ε΄ το R_s is hydrogen, R₆O₂C4_ER₆O², cyano; R₆CO-; optionally substituted lower alkyl, nitro or Y¹Y²N-;

Y¹ and Y² are independently hydrogen, alkyl, aralkyl or heteroaralkyl;

all Queria BNA era reddependently token X, bone A, and X, are independently hydrogen, B, R, N-, R, O-, FR, R, NCO-, R, R, NSO₂-,

X₆ and X₆ are independently hydrogen, B, R, N-, R, O-, FR, R, NCO-, R, R, NSO₂-,

R, CO-, halo, cyano or nitro;

25 aralkyl or optionally substituted lower alkyl or optionally substituted
25 aralkyl or optionally substituted heteroaralkyl; introduced beautified as a substituted beautified as a substituted beautified as a substituted lower alkyl, or one of R₇ and R₈ is hydrogen and the other of R₇ and R₈ is R₁₀(O)CCH₂- or lower acyl;

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n is 1.2 or 3; or the land of the land between the best of the production of the bank of the land of t

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p is 1 or 2.

a pharmaceutically acceptable salt thereof, an N-oxide thereof, a hydrate thereof or a solvate thereof.

DETAILED DESCRIPTION OF THE INVENTION

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Assused above, and throughout the description of the invention, the following terms, unless otherwise indicated, shall be understood to have the following meanings:

The odd membratic posts in a specific one of the contract of the con-

Definitions

15 "Patient" includes both human and other mammals.

green of the company "Alkyl" means an aliphatic hydrocarbon group which may be straight or branched having about 1 to about 20 carbon atoms in the chain. Preferred alkyl groups have 1 to about 12 carbon atoms in the chain. Branched means 20 that one or more lower alkyl groups such as methyl, ethyl or propyl are attached to a linear alkyl chain. "Lower alkyl" means about 1 to about 4 carbon atoms in the chain which may be straight or branched. The alkyl may be substituted with one or more alkyligroup substituents" which may be the same or different, and include halo, cycloalkyl, alkóxy, amino, acylamino, aroylamino. carboxy, alkoxycarbonyl, aralkyloxycarbonyl, heteroaralkyloxycarbonyl or 25 SEYTYNCO-swhere Ytand Yare independently-hydrogen, alkyl, aralkyl or wheteroaralkylla Exemplary alkyl groups include methyl, triffuoromethyl, cyclopropylmethyl; cyclopentylmethŷl, ethŷl; n-propyl, h-butyl, h-butyl, n-pentyl, 3-pentyl, methoxyethyl, carboxymethyl, methoxycarbonylethyl. benzyloxycarbonylmethyl, pyridýlmethyloxycarbonylmethyl.

about 3 to about 10 carbon atoms. Exemplary monocyclic cycloalkyl rings include cyclopentyl, fluorocyclopentyl, cyclohexyl and cycloheptyl. The cycloalkyl group is optionally partially unsaturated or optionally substituted by one or more halo; methylene (H2C=); alkyl; fused ary or fused heteroaryl.

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rogen, ally it and by or helandarally if preferred prenyl group substituting

Exemplary multicyclic cycloalkyl rings include 1-decalin, adamant-(1- or 2-)yl and norbornyl.

system of about 3 to about 10 ring atoms. Preferred rings include about 5 to about 6 ring atoms wherein one of the ring atoms is oxygen, nitrogen or sulfur. The heterocyclyl is optionally partially unsaturated of optionally substituted by one or more alkyl, halo, aryl, heteroaryl, fused aryl or fused heteroaryl.

Exemplary monocyclic rings include pyrrolidyl, piperidyl, tetrahydrofuranyl, tetrahydrothienyl and tetrahydrothiopyranyl. The thiotor nitrogen moiety of the heterocyclyl may also be optionally oxidized to the corresponding N-oxide, S-oxide or S,S-dioxide.

Peantions

"Ary!" means aromatic carbocyclic radical containing about 6 to about 10 15 carbon atoms. Exemplary anyl include phenyl or naphthyla or phenyl substituted or naphthyl substituted with one or more aryl group substituents which may be the same or different, where "anyl group substituent" includes hydrogen, alkyl, aryl, heteroaryl, aralkyl, heteroaralkyl, hydroxy, hydroxyalkyl, alkoxy, aryloxy, aralkoxy, acyl, aroyl, halo; nitro; cyano; carboxy اللهاة المالية 20 alkoxycarbonyl, aryloxycarbonyl, aralkoxycarbonyl, acylamino, aroylamino, 05 alkylsulfonyl, arylsulfonyl, heteroarylsulfonyl, alkylsulfinyl, arylsulfinyl, is heteroarylsulfinyl, alkylthio; arylthio, heteroarylthio; aralkylthio; or access heteroaralkylthio, fused heterocyclyl, arylazo, heteroarviazo. Y1Y2N-, Y1Y2NCO, or, Y1Y2NSO2-, where Y1 and Y2 are independently hydrogen. alkyl, aryl, aralkyl or heterogralkyl, or Y1, Y2 and N taken together form a 3 3 3 3 heterocyclyl. The aryl group substituents are as defined herein. Preferred aryl groups are optionally substituted phenyl or optionally substituted naphthyl. Preferred aryl group substituents include hydrogen, alkyl, hydroxy, acyl, aryl aroyl, aryloxy, halo, nitro, alkoxy, cyano, alkoxycarbonyl, acylamino, alkylthio, Y'Y'N-, Y'Y'NCO- or Y'Y'NSO2-, where Y' and Y' are independently 30 hydrogen, alkyl, aralkyl or heteroaralkyl; preferred phenyl group substituents are aryloxy and aryl; and preferred naphthyl group substituents are nitro, violede systemantit, filotonys coestra, cyalonenys end in stationing

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example nitrogen, oxygen or sulfur. The "heteroaryl" may also be substituted by one or more of the above-mentioned "aryl group substituents". Exemplary heteroaryl groups include pyrazinyl, furanyl, thienyl, pyridyl, pyrimidinyl, isoxazolyl, isothiazolyl, oxazolyl, thiazolyl, pyrazolyl, furazanyl, pyrrolyl, imidazo[2,1-b]thiazolyl, benzofurazanyl, indolyl, azaindolyl, benzimiddazolyl, benzothienyl, quinolinyl, imidazolyl and isoquinolinyl. Preferred heteroaryl groups in the R substituent include benzothienyl, thienyl, imidazolyl, pyridyl

- Ar¹ CONTRACTOR OF A PROPERTY OF A PARTY OF A PROPERTY OF A PROPERTY OF A PARTY OF and quinolinyl all of which may be optionally substituted. Where monocylic heteroaryl, then preferred heteroaryls include thienyl, pyridyl and furanyl. On the second query -Ongo a second of the enthe properties of them before assessed that the contract of the time.

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"Aralkyl" means an aryl-alkyl- group in which the aryl and alkyl are as previously described. Preferred aralkyls contain a lower alkyl moiety. Exemplary aralkyl groups include benzyl, 2-phenethyl and naphthlenemethyl.

"Heteroaralkyl" means a heteroaryl-alkyl- group in which the heteroaryl and alkyl are as previously described. Preferred heteroaralkyls contain a lower alkyl mojety. Exemplary heteroaralkyl groups may contain thienyl, pyridyl, and pyrazinyland or an end of a smerre of a contract of the color

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"Aralkenyl" means an aryl-alkenyl- group in which the aryl and alkenyl are as previously described. Preferred aralkenyls contain a lower alkenyl molety: (An exemplary:aralkenyligroup is 2-phenethenyl: ab viscolic enq .outiliveliduan-

"Heteroaralkenyl" means a heteroaryl-alkenyl- group in which the heteroaryl and alkenyl are as previously described. Preferred heteroaralkenyls contain a lower alkenyl moiety Exemplary heteroaralkenyl groups may contain thienyl, pyridyl, imidazolyl and pyrazinyl. 36

30 and "Hydroxyalkyl" means a HO-alkyl- group in which alkyl is as previously defined. Preferred hydroxyalkyls contain lower alkyl. Exemplary hydroxyalkyl groups include hydroxymethyl and 2-hydroxyethyl.

"Alkexycarbony" means an arkyl-C CD- group. Exempthry

"Y" No means a substituted or unabulitated amino grada, when

"Acyle means/an H-CO or alkyl-CO group in which the alkyl group is as previously described. Preferred acyls contain a lower alkyl. Exemplary acyl

petrice groups include formyl, acetyl, propanoyl, 2-methylpropanovl, butanovl and waligim palmitoyleuritades georg grayl grand abov eme ito each to see a sno yell heterosiyi groups aronde cyterinyk furchyk thianyk pyadyk, pyrimidinyk YOTYO "Aroy!" means an aryl-ÇO group in which the alkyl group is as 5 previously described. Exemplary groups include benzovi and 1- and 2banze' henyl, quantitatyl, imidazolyl and ischaendinyl. Prefelyodiddan uve groups in the Reubeline of molude benzothierty), this by this light, compyl "Alkoxy" means an alkyl-O- group in which the alkyl group is as previously described. Exemplary alkoxy groups include methoxy, ethoxy, 10 > n-propoxy; i-propoxy; n-butoxy and heptoxy; during it its lynilo may bear monocytic heterogryl, then preferred heteroaryls include thianyl, pyridylished "Aryloxy" means an aryl-O- group in which the aryl group is as 1111 previously described. Exemplary aryloxy groups include phenoxy and "Aralky!" means an aryl-alkyl- group in which the aryl-wanthqan, a cit previously described. Preferred aralleyls contain a lower alkyl molety hypromodeld: "Aralkyloxy", means an aralkyl-Op group in which the aralkyl groups is as previously described. Exemplary aralkyloxy groups include benzyloxy and 1-ந்து திரை 2₅naphthalenemethoxyக்கு முக்கு கிக்காக மிழ்க்க கொளிய விழக்க கொளிய விழக்க கொளிய விழக்க கொளிய விழக்க and alky are as previously ledaribed. Preferred hateroaralkyls contain a lawy-20 Annua WAkylthio" means an alkyl-S-"group in which the alkyl group is as previously described. Exemplary alkylthio groups include methylthio, ethylthio, i-propylthio and heptylthio. "Aralkany" means an aryi-alkeny i group in water our eryl and stormer Types to research and anyles group in which the aryligroup is as previously described. Exemplary arylthio groups include phenylthio and 25 naphthylthio. Here overlies out means a heteropyl-plicated in which ins क्षेत्र क्षेत्र का व्यक्ति Aralkylthio! means an aralkyl-Se group in which the aralkyl group is as previously described: An exemplary aralkylthic group is benzylthic. 1990 contain thisnyl, byribyl, mudazolył and byrasigen. 30 "Y3Y4N-" means a substituted or unsubstituted amino group, wherein Y3 and, Y4 are as, previously described a Exemplary groups include amino (H2N-)? கள்கு அ**methylamino,sethylmethylaminoadimethylamino-and diethylamino**.என்றி graigs include hy carryclated and z-hydrogyedryc. "Alkoxycarbonyl" means an alkyl-O-CO- group. Exemplary 35

alkoxycarbonyl groups include methoxyc and ethoxycarbonyl, oA

in the sweet among a continuent of theoretical information

"Aryloxycarbonyl" means an aryl-O-CO- group. Exemplary aryloxycarbonyl groups include phenoxy- and naphthoxycarbonyl.

"Aralkoxycarbonyl" means an aralkyl-O-CO-'group. An exemplary aralkoxycarbonyl group is benzyloxycarbonyl.

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The state of the s

"Y³Y⁴NCO-" means a substituted or unsubstituted carbamoyl group, wherein Y³ and Y⁴ are as previously described. Exemplary groups are carbamoyl (H2NCO-) and dimethylaminocarbamoyl (Me2NCO-).

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"Y³Y⁴NSO2-" means a substituted or unsubstituted sulfamoyl group, wherein; Y³ and Y⁴ are as previously described. Exemplary groups are aminosulfamoyl (H2NSO2-) and dimethylaminosulfamoyl (Me2NSO2-).

15 Angles "Acylamino" is an acyl-NH-igroup wherein acyl is as defined herein.

"Aroylamino" is an aroyl-NH- group wherein aroyl is as defined herein.

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"Alkylsulfonyl" means an alkyl-SO₂- group. Preferred groups are those in which the alkyl group is lower alkyl.

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"Alkylsulfinyl" means an alkyl-SO- group. Preferred groups are those in which the alkyl group is lower alkyl.

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"Arylsulfonyl" means an aryl-SO2-(group) as his section with section w

in providing the certain cubattlaten will $X_{ij}(\lambda)$

The logistic "Arylsulfinyl" means an aryl-SO- group. (4) 43

"Halo" means fluoro, chloro, bromo, or iodo. Preferred are fluoro, chloro or bromo, and more preferred are fluoro or chloro.

Preferred Embodiments

A preferred embodiment of the invention is a method for treating a patient suffering from a physiological disorder capable of being modulated by inhibiting an activity of Factor Xa by administering a therapeutically effective amount of a compound of formula I.

'Anyloxyperbonythines is an anti-0-00- group. Exemplory

Jyr. A preferred compound aspect of the invention is the compound of formula I wherein R₃ is optionally substituted phenyl, optionally substituted optionally substituted benzothienyl.

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Another preferred compound aspect of the invention is the compound of formula; wherein n is, 1, and m is, 1, and a cose " COM* " "

cherein 22 and 27 are as previously despribed. Exempliary proups the

Another preferred compound aspect of the invention is the compound of formula I wherein X₂ and X₂, taken together are oxo.

* Yay NSO2* means a substituted or unsubstituted sulfernoy! group,

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15 in the compound aspect of the invention is the compound of formula I wherein X_s and X_s, taken together are =NH.

"Aroyland to" is an atoyle'lith group wherein ercyl is as defined harein

Another preferred compound aspect of the invention is the compound of formula I wherein X_5 and X_5 taken together are $=NR_5$ wherein R_5 is $R_6O_2C_5$.

દ ે ાત which the alkyl લાગાંગ is lower વર્ષિયા.

Another preferred compound aspect of the invention is the compound of Alk, it and Not in each substitution of the property of the invention is the compound of the invent

which the aikyl arcup is laver alkyl

formula I wherein is phenyl and the carbon substituted with X_s , X_s and HR_2N - is attached to the 3-position of the phenyl $X^{(1)}$ is attached to the 3-position of the phenyl $X^{(1)}$

Another preferred compound aspect of the invention is the compound of

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Another preferred compound aspect of the invention is the compound of formula I wherein R is hydrogen, methyl, aralkyl, heteroaralkyl, HO₂CCH₂-, $HOC(O)CH_2$ -, $H_2NC(O)CH_2$ -, (aralkyl) $HNC(O)CH_2$ - or (heteroaralkyl)HNC(O)CH2-. Another preferred compound aspect of the invention is the compound of formula I wherein X, is hydrogen and X, is carboxyalkyl, alkoxycarbonylalkyl or aryl, or X, and X, taken together form oxo... Another preferred compound aspect of the invention is the compound of formula I wherein R₁ is R₃SO₂-.. The state of a same of years Another preferred compound aspect of the invention is the compound of formula I wherein R₁ is R₃R₄NSO₂-. Another preferred compound aspect of the invention is the compound of claim 1 wherein one of X₆ and X₆ is amino in a para position relative to the English the second of the second of the second of the NHR₂ molety. With the control of the second of the secon Species according to the invention are selected from the group econsisting of: calcastic tell banks by the action of the discretization of a Naphthalene-2-sulfonic acid {1-[3-(aminoiminomethyl)benzyl]-2-oxopyrrolidin-3-(S)-yl]amide trifluoroacetate; proporting the analysig 84-8 labilion page. Dibenzofuran-2-sulfonic acide [1-[3-(aminoiminomethyl)benzyl]-5-oxopyrrolidin-3-yl}amide trifluoroacetate; efect all position entires (2)-8 US Toluene-4-sulfonic acid {1-[3-(aminoiminomethyl)benzyl]-2-oxopyrrolidin-3-(S)-yl)amide trifluoroacetate;statolesprouths, on a physical Elements 3,4-Dihydro-1H-isoquinoline-2-sulfonic acid (1-[3-(aminoiminomethyl)benzyl]-

2-oxopyrrolldin-3-(S)-yl]amide trifluoroacetate#fit al. an spittern(+ 16)-8

மாயா அ3'-Methoxy-biphenyl-4-sulfonic acid {1-[3-(amliñoimhinomhifhyl)benzyl]-2-
-ुं roxopyrrolidin-3-(S)-yl}amide trifluoroacetate; प्रति हा विवासनाविक किल्लाकी
$HOO(O)O(1_2 \gamma, H_2NC(O)OH_2 \gamma, (araikyl)HNG(O)(C(1_2 \gamma O))$
Naphthalene-1-sulfonic acid {1-[3-(aminoiminomethyl)benzyl]-2-oxopyrrolidir
5 3-(S)-yl)amide trifluoroacetate;
Another, stend of about aspect of the invention is the compound
5-Pyrid-2-ylthlophene-2-sulfonic acid (1-[3-(aminoiminomethyl)benzyl]-2-oxopyrrolidin-3-(S)-yl}amide trifluoroacetate;
10世紀 Biphenyl-4-sulfonic acid {1-[3-(amihoiminomethyl)的
ວກຄວາ້ໃ-Methoxynaphthalene-2-sulfonic acid (1-[3-(aminoiminomethyl)benzyl]-2- oxopyrrolldin-3-(S)-yl)amide trifluoroacetate; ອີກສາຄາຄານ ໄດ້ເຄັນຕາວັນ
15
ະນາພວ7-Ethoxynaphthalene-2-sulfonic acid {1-[3-(aminoiminomethyli)benzyl]-2-
் அற்oxopyrrolidin-3-(S)-yl}amide trifluoroacetate; அரசை வரச்சல் உள்ள
5-Chloro-6-methoxynaphthalene-2-sulfonic acid {1-[3-20] (aminoiminomethyl)benzyl]-2-oxopyrrolidin-3-(S)-yl}amide trifluoroacetate;
5-Chloro-6,7-dimethoxynaphthalene-2-sulfonic acid-{1-[3=e againate triflüõroacetate;
25. ஆ7-Aminonaphthalene-2-sulfonic acid {1-[3-(aminoimiñomethyl)bentzýl]-2- oxopyrrolidin-3-(S)-yl}amide bistrifluoroacetate; சொகிய கொகிர் பி-டி
Naphthalene-2-sulfonic acid {1-[4-(aminoiminomethyl)benzyl]-2-oxopyrrolidin
3-(S)-yl}amide trifluoroacetate; jefstensonomitt abm som 3
7-Methoxynaphthalene-2-sulfonic acid [1-(3-aminomethylbenzyl)-2-
oxopyrrolidin-3-(S)-yl]amide trifluoroacetate நிற்கு உட்டும் கிங்கிக்கு - பிர
Naphthalene-2-sulfonic acid {1-[3-(aminoiminomethyl)benzyl]-2-oxopyrrolidin-
35 3-(S)-yl}methyl amide trifluoroacetate;Bir obinteriy-(8)-8-ndbil@byor ko-S

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Naphthalene-2-sulfonic acid {1-[3-(aminoiminomethyl)benzyl]pyrrolidin-3-(S)yl}amide bistrifluoroacetate:

7-Methoxynaphthalene-2-sulfonic acid {1-[3-(aminoiminomethyl)benzyl]-2,5dioxopyrrolidin-3-(S)-yl}amide trifluoroacetate;

Naphthalene-2-sulfonic acid (1-[3-(aminoiminomethyl)benzyl]-2-oxopiperidin-3-yl}amide trifluoroacetate;

7-Methoxynaphthalene-2-sulfonic acid {1-[3-(aminoiminomethyl)benzyl]-2-oxo-10 azepan-3-(S)-yl}amide trifluoroacetate: '

7-Methoxynaphthalene-2-sulfonic acid {1-[3-(aminoiminomethyl)benzyl]-2oxopyrrolidin-3-(S)-yl}methyl amide trifluoroacetate:

6-Methoxynaphthalene-2-sulfonic acid {1-[3-(aminoiminomethyl)benzyl]-2oxopyrrolidin-3-(S)-yl}amide trifluoroacetate:

6-Methoxynaphthalene-2-sulfonic acid {1-[3-(aminoiminomethyl)benzyl]-2-20 oxopyrrolidin-3-(S)-yl}methyl amide trifluoroacetate:

2-[{1-[3-(Aminoiminomethyl)benzyl]-2-oxopyrrolidin-3-(S)-yl}-6methoxynaphthalene-2-sulfonylamino]-N-phenethylacetamide trifluoroacetate; ermer amounts show ally (B) Posterom, term

25 9,10-Dioxo-8a,9,10,10a-tetrahydroanthracene-2-sulfonic acid {1-[3-(aminoiminomethyl)benzyl]-2-oxopyrrolidin-3-(S)-yl)amide trifluoroacetate; connected metal/free cycle, exergerelidin-3-(Seyl)amic constituoreacer re-

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8-Chloro-7-methoxynaphthalene-2-sulfonic acid {1-[3-(aminoiminomethyl)benzyl]-2-oxopyrrolidin-3-(S)-yl}amide trifluoroacetate: whateou nouthield our metry. First with a poor a

7-Methoxynaphthalene-2-sulfonic acid {1-[4-(aminoiminomethyl)benzyl]-2oxopyrrolidin-3-(S)-vi)amide trifluoroacetate: and consultated commetty-(2) and the property of the contraction of th

6,7-Dimethoxynaphthalene-2-sulfonic acid {1-[3-(aminoiminomethyl)benzyl]-2oxopyrrolidin-3-(S)-ŷl}amidêftriflûöroacetate: The paicet manaît la fill in 35 can now with a copy of the proposition of (3)-yilling animal

Naphtho(2,3-d)-(1,3)dioxole-6-sulfonic acid {1-[3-(aminoiminomethyl)benzyl]-2-oxopyrrolidin-3-(S)-yl)amide trifluoroacetate: as we firm a reliability 7-Benzyloxynaphthalene-2-sulfonic acid {1-[3-(aminoiminomethyl)benzyl]-2oxopyrrolidin-3-(S)-yl)amide trifluoroacetate; [yu 23-2 mbitorioxo b 7-Hydroxynaphthalene-2-sulfonic acid {1-[3-(aminoiminomethyl)benzyl]-2oxopyrrolidin-3-(S)-yl}amide trifluoroacetate; a notion with ablantilly of 6-Hydroxynaphthalene-2-sulfonic acid (1-[3-(aminoiminomethyl)benzyl]-29 oxopyrrolldin-3-(S)-yl]amide trifluoroacetate; w/ sbirnelly-48)-8-diagram 5-Chioro-3-methylbenzo[b]thiophene-2-sulfonic acid {1-[3-ny-orderM-7] (aminoiminomethyl)benzyl]-2-oxopyrrolidin-3-(S)-yl}amide trifluoroacetate: 15 5-Chloro-3-methylbenzo[b]thiophene-2-sulfonic acid (1-[3-ny-to-rish a (aminoiminomethyl)benzyl]-2-oxopyrrolidin-3-(S)-yl}methyl-amide trifluoroacetate: 2 No. Carchaputharane-2-sulfonia ama 11-(3-jand phalmometry) prestyl 7-Methylnaphthalene-2-sulfonic acid {1-[3-(aminoiminomethyl)benzyl]-2- 05 20 oxopyrrolidin-3-(S)-yl}amide trifluoroacetate: -8-1 -(31-E-million vacor Sthysis d(hp.) - continuation A) 47-11) -7-Ethylnaphthalene-2-sulfonic acid/{1-[3-(aminoiminomethyl)benzyl]-2oxopyrrolidin-3-(S)-yl}amide trifluoroacetate; 25 9.10-Cross stage 10.10est dealydroantifed no-9-surunic acts 140-..... 5-Chloro-6-aminonaphthalene-2-sulfonic acid {1-[3-, ynternon-montime) (aminoiminomethyl)benzyl]-2-oxopyrrolidin-3-(S)-yl)amide bistrifluoroacetate; 8-Only a Z-methody partial and a local partial solution and the solution of th 7-Methylaminonaphthalene-2-sulfonic acid (1-[3-(aminoiminomethyl)benzyl]-2oxopyrrolidin-3-(S)-yl}amide bistrifluoroacetate; 30 Para enadifythermorae unime) Elementing over the expense smiller in Schille A. A. (aminoiminomethyl)benzyl]-2-oxopyrrolidin-3-(S)-yl}amide bistrifluoroacetate; A Program of the empire representation of the Property of the program of the prog 1,2,3,4-Tetrahydroisoquinolinyl-7-sulfonic acid {1-[3-12] - Valoution (quino (aminoiminomethyl)benzyl]-2-oxopyrrolidin-3-(S)-yl)methyl amide dihydrochloride;

10.

- 7-Methoxynaphthalene-2-sulfonic acid {1-[3-(aminoiminomethyl)benzyl]-2-oxopyrrolidin-3-(S)-yl}-(4-nitrobenzyl)amide trifluoroacetate;
- 5 7-Methoxynaphthalene-2-sulfonic acid {1-[3-(aminoiminomethyl)benzyl]-2-oxopyrrolidin-3-(S)-yl}-(4-aminobenzyl)amide bistrifluoroacetate;

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- 7-Methoxynaphthalene-2-sulfonic acid {1-[3-(aminoiminomethyl)benzyl]-2-oxopyrrolidin-3-(S)-yl}(3-nitrobenzyl)amide trifluoroacetate;
- 7-Methoxynaphthalene-2-sulfonic acid {1-[3-(aminoiminomethyl)benzyl]-2-oxopyrrolidin-3-(S)-yl}(3-aminobenzyl)amide bistrifluoroacetate;
- 7-Methoxynaphthalene-2-sulfonic acid {1-[3-(aminoiminomethyl)benzyl]-2-oxopyrrolidin-3-(S)-yl}-(2-nitrobenzyl)amide trifluoroacetate;
 - 3-[2-Oxo-3(S)-(2-phenylethenesulfonylamino)pyrrolidin-1-ylmethyl]-benzamidine trifluoroacetate;

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- 20 3-[2-Oxo-3(S)-(2-phenylethanesulfönylamino)pyrrolidin-1-ÿlmethyl]- benzamidine trifluoroacetate;
 - [Imino-(3-{3-[7-Methoxynaphthalene-2-sulfonyl)methylamino]-2-oxo-3(S)-pyrrolidin-1-ylmethyl]phenyl)methyl]carbamic acid ethyl ester;
- 25xu-Squarad(ivarent amioruma) (pt) bias olnotiva anticularis successor anticoloris of Squarad (pyridin-4-ylamino)-ethanesulfonylamino)-pyrrolidin-1-ylmethyl]-benzamidine bistrifluoroacetate;

 9-figureq(i), as no information to the approximation of some serious serious
- 2'-Methoxybiphenyl-4-sulfonic acid (1-[3-(aminoiminomethyl)benzyl]-2-30 oxopyrrolidin-3(S)-yl} amide trifluoroacetate;
- 35 Isoquinolinyl-5-Sulfonic acid (1-[3-(aminoimiñomethyl)benzyl]-2-oxo-3(S)- pyrrolidin-3-yl}amide bistrifluoroacetate;

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• %	exopy referred is, right-numberizyljamice trillings cetate:	
	2,4-Diaminoquinazoline-6-sulfonic acid {1-[3-(aminoiminomethyl)benzyl]	2-
5	.π. οχο-3(S)-pyrrolidin-3-yl}amide) trifluoroacetate; -s. s.s.dmqsny/ *πείνε.	
~2.	excepts attain and a subject to almoneury) accuract sent acromosticus;	}
	7-Methoxy-2-naphthalenesulfonic acid {1-[3-(aminoiminomethyl)benzyl]-2)-0Y/
٠	3(S)-pyrrolidin-3-yl)ethylamide trifluoroacetate; and still damp units 4-7	. 020
	oxopymoration2-(kg/gt) 3 nationeray.) and the three reseatates	
10	7-Methoxy-2-napthalenesulfonic acid {1-[3-(aminoiminomethyl)benzyl]-2-	οχό-
Ω.	3(S)-pyrrolidin-3-yl)(3-fluorobenzyl)amide trifluoroacetate;suyxonisM-v	
	exopyrmidia-3-(5) gl/(3-aminobenzyl)amide patrilledroacetate.	
	7-Methoxy-2-napthalenesulfonic acid {1-[3-(aminoiminomethyl)benzyl]-2-	охо-
$\cdot \mathfrak{C}$	3(S)-pyrrolidin-3-yl}(4-methylbenzyl)amide trifluoroacetate; weddeM-3	
15	empty:/phdin-3-(S)-yi)-(2-nitrapenzyi)amide trifluoroedetate;	i5
	7-Methoxy-2-napthalenesulfonic acid {1-[3-(aminoiminomethyl)benzyl]-2-c	oxo-
•	3(S)-pyrrolidin-3-yl}(3-methylbenzyl)amide trifluoroacetate	
	, significant this property of the second state of the second sec	
	7-Methoxy-2-napthalenesulfonic acid {1-[3-(aminoiminomethyl)benzyl]-2-c	OXC-
20	3(S)-pyrrolidin-3-yl}napthalene-2-ylmethylamide trifluoroacetate; (5-5)	Q5
	erojaceorusi iri saibinsaner	
	7-Methoxy-2-napthalenesulfonic acid {1-[3-(aminoiminomethyl)benzyl]-2-c	XO-
	3(S)-pyrrolidin-3-γl}(3-phenylallyl)amide trifluoroacetate; η-30-ο ο ο	
O.E.	getunijde- reynmetrijijphenyterethyljoarbarnie acid stiryt getad.	
25	7-Methoxy-2-napthalenesulfonic acid (1-[3-(aminoiminomethyl)benzyl]-2-c	XÕ-
	3(S)-pyrrolidin-3-yl)(3-methylbenzyl)amide trifluoroacetate;3):-cvC 2-6	
	when the properties the properties are selected as the properties and the properties are the properties and the properties are	
	7-Methoxy-2-napthalenesulfonic acid {1-[3-(aminoiminomethyl)benzyl]-2-0	XO-
30	3(S)-pyrrolidin-3-yl)(2-fluorobenzyl)amide trifluoroacetate; poy code in a	
	-ಪೂರ್ಣಿಯಾಗಳಿಗೆ ಅದ್ದೇವರ್ (ಚಿ)ಕ್ಕಿ ಸರ್ವಾಗಳಿಗಳು 2-Fluorobiphenyl-4-sulfonic acid {1-[3-(aminoiminomethyl)benzyl]-2-охо-3	
	pyrrolidin-3-yl)methylamide trifluoroacetate; din productivine in the periodic actions and the productivine in the periodic action of the productivine in the periodic action of the pe	(3)-
7 P.	ાન્દ્રાન્ટ્રાં તે તેમાં તેમાં તેમું ઉત્તરીની ત્રાપ્યુ-(ઉ)ઈ ક્ષ્યલ-દ્ર-તીપુદ્રના દો (viberrenic desert દો - 3-[{1-[3-(Aminoiminomethyl)benzyl]-2-oxopyrrolidin-3(S)-3-yl}-(7-	
35	methoxynaphthalene-2-sulfonyl)amino]proplonamide trifluoroacetate;	
		πů
	perclassemouth law, ablir ally-finiteening	

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- 2-[{1-f3-(Aminoiminomethyl)benzyl]-2-oxopyrrolidin-3-(S)-yl}naphthalene-2sulfonylamino]-N-phenethylacetamide trifluoroacetate:
- 2-[{1-[3-(Aminoiminomethyl)benzyl]-2-oxopyrrolidin-3-(S)-yl}biphenyl-4sulfonylamino]-N-phenethylacetamide trifluoroacetate; . . . 5
 - 2-[{1-[3-(Aminoiminomethyl)benzyl]-2-oxopyrrolidin-3-(S)-yl}-7methoxynaphthalene-2-sulfonylamino]-N-phenethylacetamide trifluoroacetate:

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- 10 2-[{1-[3-(Aminoiminomethyl)benzyl]-2-oxopyrrolidin-3-(S)-yl}-7methoxynaphthalene-2-sulfonylamino]-N-ethylacetamide trifluoroacetate;
 - 2-[{1-[3-(Aminoiminomethyl)benzyl]-2-oxopyrrolidin-3-(S)-yl}-7methoxynaphthalene-2-sulfonylamino]-N,N-dimethylacetamide trifluoroacetate: Similar is a suggest of the significant of the tatesmore trender
 - 2-[{1-[3-(Aminoiminomethyl)benzyl]-2-oxopyrrolidin-3-(S)-yl}-7methoxynaphthalene-2-sulfonylamino]-N-benzylacetamide trifluoroacetate; CHEROLOGY OF A SHORE IVERY OF A CONTROL OF A
- 2-[{1-[3-(Aminoiminomethyl)benzyl]-2-oxopyrrolidin-3-(S)-yl}-7-20 methoxynaphthalene-2-sulfonylamino]-N-(2-p-toluvlethyl)acetamide trifluoroacetate; and 35 alare before After Such a direct verdgange of tem
- 2-[{1-[3-(Aminoiminomethyl)benzyl]-2-oxopyrrolldin-3-(\$)-vi)-7methoxynaphthalene-2-sulfonylaminoj-N-(3-phenylpropyl)acetamide trifluoroacetate: 25 islands ynaphthalana-ti-rullonid acid (1-[5-(ai tholminumarryi)canzyl)-2 ord-
- 2-[{1-[3-(Aminoiminomethyl)benzyl]-2-oxopyrrolidin-3-(S)-vil-7methoxynaphthalene-2-sulfonylamino]-N-(4-methylbenzyl)acetamide And the individual transfer and the state of the comomic states are supplied to the states of the st etalable, outin ohim styrnadily-(8)8- sibbatic
 - 2-[{1-[3-(Aminoiminomethyl)benzyl]-2-oxopyrrolidin-3-(S)-yl}-7methoxynaphthalene-2-sulfonylaminoj-N-[2-(3-flubrophenyl)ethyljacetamide benzyll 2-oxopymolidin-3(5)-yljamida trifuoroacetale trifluoroacetate:
- 35xc- 2-[{1-[3-(Aminoiminomethyl)benzyl]-2-oxopyrrolidin-3-(\$)-yl)-7-01-04-1 methoxynaphthalene-2-sulfonylamino]-N-indan-2-ylacetamide trifluoroacetate:

् ४ स्म	methoxynaphthalene-2-sulfonylamino]-N-(2-pyridin-3-yl-ethyl)acetamide bistrifluoroacetate;	
5	h-tynedold(ty-(كاجن nibdor yyoxo-S-(tys-ed(tyde-contimio-anA)-ق)- المارة المار	2- - 0x0
	-7, iv-(8)-6-mail: yaoxu-s-fivsneo(lyikamanimianim4 - 1;-1}}-s -4,5-Dichlorothiophene,-2-sulfonic acid {1-[3-(aminoiminomethyl)benzŷl]- 3(S)-pyrrolidin-3-yl}-methylamide trifluoroacetate;	2-oxc
10	2-([1-(3-)Amaciminarethyl)benzvlj-2-ozopvrolidin-3-(S)-yl)-7- 2-[lýzńadophophope-2-sulfonic acid:(1-[3-(aminoiminomethyl)benzyl]-2-(aminoiminomethyl)benzylamide trifluoroacetate;	⊖ 2- охо -
ระบองค 15	-7-{ly-(2\ 8-niclic ayacso-2-llys as divide modimic cimA)-8}-1)} 2 <u>7-Methoxy-2-napthalenesulfonic acid {1-[3-(aminoiminomethyl)benzyl]-2</u> 3(S)-pyrrolidin-3-yl}-2-cyclopropylphenethylamide trifluoroacetate:	- охо- 15
्र १७ १३		•
20	-7-{hy-(3)-8-nibbonyqoxe-S-fivxns a(lydismonimonimonimo)-8}-1)}-9 3-[{d ₁ -[3 ₃ (Aminoiminomethyl)benzyl]-2-oxopyrrolidin=3(S)+3-yl}-(7-cd.ommethoxynaphthalene-2-sulfonyl)amino]acetamide trifluoroacetate; 33-4	<i>0</i> 8
25	3-[{1-[3-(Aminojminomethyl)benzyl]-2-oxopyrrolidin-3(S)-3-yl}-(7-)-1}]-5 methoxynaphthalene-2-sulfonyl)amino]-2-methylacetamide trifluoroacetar	t e; ö§
20	7-Methoxynaphthalene-2-sulfonic acid (1-[3-(aminoiminomethyl)benzyl]-2 azetidin-3(S)-yl}amide,trifluoroacetate;ned(lydiemon minoimino-c]-t)}-S	
30	epiniocos(lysnedlyritem b) M-(onims/yeotlus-S-baels tingenyxodlee 7-Methoxynaphthalene-2-sulfonic acid {1-[3-(aminoiminomethyl)benzyl]-2 azetidin-3(S)-yl}benzylamide trifluoroacetate;	-охо- (*/*)
£17 ¹)	tiv (2)-cib form goxo 2-flyznadityrdamoreo (c./mA)-8)-11)-9 .5,6,7,8-Tetrahydronaphthalene-2-sulfonic acid (1-[3-(aminoiminomethyl)-benzyl]-2-oxopyrrolidin-3(S)-yl]amide trifluoroacetate; (elalocencia)	
35 916170	7-Methoxy-2-napthalenesulfonic acid/{1-[3-(aminoiminomethyl)benzyl]-2-c3(S)-pyrrolidin-3-yl}-(2-methoxybenzyl)amide trifluoroacetate:	÷oxo÷

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- 7-Methoxy-2-napthalenesulfonic acid {1-[3-(aminoiminomethyl)benzyl]-2-oxo-3(S)-pyrrolidin-3-yl}-(3-methoxybenzyl)amide trifluoroacetate;
- 7-Methoxy-2-napthalenesulfonic acid (1-[3-(aminoiminomethyl)benzyl]-2-oxo-3(S)-pyrrolidin-3-yl}-(4-methoxybenzyl)amide trifluoroacetate;
 - 7-Methoxy-2-napthalenesulfonic acid {1-[3-(aminoiminomethyl)benzyl]-2-oxo-3(S)-pyrrolidin-3-yl}(pyridin-2-ylmethyl)amide trifluoroacetate;
- 7-Methoxy-2-napthalenesulfonic acid {1-[3-(aminoiminomethyl)benzyl]-2-oxo-3(S)-pyrrolidin-3-yl}(pyridin-3-ylmethyl)amide trifluoroacetate;
 - 7-Methoxy-2-napthalenesulfonic acid {1-[3-(aminoiminomethyl)benzyl]-2-oxo-3(S)-pyrrolidin-3-yl}(pyridin-4-ylmethyl)amide trifluoroacetate;
 - 7-Methoxy-2-napthalenesulfonic acid {1-[3-(aminoiminomethyl)benzyl]-2-oxo-3(S)-pyrrolidin-3-yl}-(1-benzyl-1H-imidazol-2-ylmethyl)amide trifluoroacetate;
- (1-Methyl-1H-imidazol-2-yl)benzene-4-sulfonic acid {1-[3-20 (aminoiminomethyl)benzyl]-2-oxopyrrolidin-3(S)-yl)amide trifluoroacetate;
 - 7-Methoxy-2-napthalenesulfonic acid (1-[3-(aminoiminomethyl)benzyl]-2-oxo-3(S)-pyrrolidin-3-yl}-(3-hydroxybenzyl)âmide trifluoroacetate;
- 25 7-Methoxy-2-napthalenesűlfönic acid (1-[3-(aminoiminomethyl)benzyl]-2-oxo-3(S)-pyrrolidin-3-yl}-(2-hýdroxýbenzyl)amide trifluoroacetate;
 - 7-Methoxy-2-napthalenesûlfonic acid (1-[3-(aminoimlnomethyl)benzyl]-2-oxo-3(S)-pyrrolidin-3-yl)(pyrazol-3-ylmethyl)amide trifluoroacetate;
- Quinoline-6-sulfonic acid {1-[3-(aminoiminomethyl)benzyl]-2-oxopyrrolidin-3-(S)-yl}amide trifluoroacetate;
- 4-Pyridin-4-ylbenzene sulfonić acid (1-[3-(aminolminomethyl)benzyl]-2-35 oxopyrrolidin=3(S)-yl}amide bistrifluoroacetate;

-C. X Ü+	3(S)-pyrrolidin-3-yl)(thiophene-2-ylmethyl)amide trifluoroacetate;
·თ. ··· 5	4-Pyridin-3-ylbenzene-sulfonic acido{1-[3-(aminoiminomethyl)benzyl]-2- oxopyrrolidin-3(S)-yl}amide bistrifluoroacetate; ո-4)-ա-Չ ունիսի ա-(Հ)Տ c
28 ⁶	N-Methylpyrid-4-ylphenyl-4-sulfonic-acid-{1-[3-(aminoiminomethyl)benzyl]-2-oxopyrrolidin-3(S)-yl}amide_trifluoroacetate; hbhyarin a nibiloayq-(3)-
10 -0x3	2-Methoxyquinoline-7-sulfonlo acid [1-[3-(aminoiminomethyl)benzyl]-2-7 - 2-Methoxyquinoline-7-sulfonlo acid [1-[3-(aminoiminomethyl)benzyl]-2-7 - 0xopyrrolidin-3-(S)-yl)amide trifluoroacetate; albinyd)(ly-6-albinyd)(S)&
.∵∋ 15	4-(6-Methoxypyridin-2-yl)benzene-4-sulfonic; acid; {1-[3-180-500-6M-7-6-15-180(lyny)benzyl]-2-oxopyrrolidin-3(S)-yl)amide-bistrifluoroacetate;
joy i	4-(3-Chloropyridin-2-yloxy)benzene-4-sulfonic acid (1-[3-1.3-vxodbalk-) (aminoiminomethyl)benzyl]-2-oxopyrrolidin-3(S)-yl}amide trifluoroacetate;
20	4-(N-Oxidopyridin-3-yl)benzene-4-sulfonic acid (1-[3-1]: mi-11-lydia (1-1) (aminoiminomethyl)benzyl]-2-oxopyrrolidin-3(S)-yl)amide trifluoroacetate;
, ox	4-Phenoxybenzene-4-sulfonic acid (1,-[3-(amingiminomethyl)benzyl]-2 oxopyrrolidin-3(S)-yl} amide trifluoroacetate; abyd-3)-(1,-8-mbitonyd-(5-0
25 	7-Methoxy-2-napthalenesulfonic acid (1-[3-(aminoiminomethyl)benzyl]-2-oxo-3(S)-pyrrolidin-3-yl)(thiophen-3-ylmethyl)amide trifluoroacetate;
30	6-Methoxynaphthalene-2-sulfonic acid (1-[3-(methoxyaminoiminomethyl)-benzyl]-2-oxopyrrolidin-3-(S)-yl)methylamide trifluoroacetate;
٠٠.	6-Methoxynaphthalene-2-sulfonic acid {1-[3-(cyanoaminoiminomethyl)benzyl]- 2-oxopyrrolidin-3-(S)-yl)methylamide trifluoroacetate:
35	6-Methoxynaphthalene-2-sulfonic acid (1-[3-(hydroxyaminoiminomethyl) benzyl]-2-oxopyrrolidin-3-(S)-yl}-methylamide trifluoroacetate;

- 4-Amino-3-[3-(S)-(7-methoxynaphthalene-2-sulfonylamino)-2-oxopyrrolidin-1-yl-methyl]benzamidine dihydrochloride;
- 4-Amino-3-[3-(S)-(7-methoxynaphthalene-2-sulfonylmethylamino)-2-oxopyrrolidin-1-yl-methyl]benzamidine trifluoroacetate;
 - N-(4-Carbamimidoyl-2-{3-[(7-methoxynaphthalene-2-sulfonyl)methylamino]-2-oxopyrrolidin-1-(S)-ylmethyl}phenyl)acetamide trifluroacetate;
- 4-Amino-3-[3-(S)-(4-tert-butylbenzenesülfonylamino)-2-oxopyrrolidin-1-yl-methyl]benzamidine trifluoroacetate;
 - 3-Amino-5-[3-(S)-(7-methoxynaphthalene-2-sulfonylamino)-2-oxopyrrolidin-1-yl-methyl]benzamidine bistrifluoroacetate;
 - {4-(Aminoiminomethyl)-2-[3-(7-methoxynaphthalene-2-sulfonylamino)-2-oxopyrrolidin-1-ylmethyl]phenoxy}acetic acid methyl ester trifluoroacetate;
- {4-(Aminoiminomethyl)-2-[3-(7-methoxynaphthalene-2-sulfonylamino)-2-oxopyrrolidin-1-ylmethyl]phenoxy}acetic acid trifluoroacetate;
- 25% 64-[3-(S)-(7-Methoxynaphthalene-2-sulfonýlamiho)-2-oxôpýrfolidíh-1-ylmethyl]-thiophene-2-carboxamidine trifluóroacetate;
- 14-{3-(S)-[(7-Methoxynaphthalene-2-sulfonyl)methylamino]-2-oxopyrrolidin-1-ylmethyl)thiophene-2-carboxamidine trifluoroacetate;
 - 2-[[1-(5-Carbamimidoylthiophene-3-ylmethyl)-2-oxopyrrolidin-3-(S)-yl](7-methoxynaphthalene-2-sulfonyl)amino]acetamide trifluoroacetate;
- 4-{3-(S)-[(7-Methoxynaphthalene-2-sulfonyl)benzylamino]-2-oxopyrrolldin-1-35% ylmethyl)thiophene-2-carboxamidine trifluoroacetate; a valent boxamidine trifluoroacetate;

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- 4-[3-(S)-(5-Chloro-3-methylbenzo[b]thiophene-2-sulfonylamino)-2-oxo-pyrrolidin-1-ylmethyl]thiophene-2-carboxamidine trifluoroacetate
- 5-[3-(\$)-[(7-Methoxynaphthalene-2-sulfonyl)methylamino]-2-oxopyrrolidin-1ylmethyl}thiophene-3-carboxamidine trifluoroacetate; անակագործ մ
- 4-{ع-(S)-[(ر5-Chloro-3-methylbenzo[b]thiophene-2-sulfonyl)benzylamiño]-2oxopyrrolldin-1-ylmethyl}thiophene-2-carboxamidine-trifluoroacetate:
- 10 4/6/3/(S)-[(Methanesulfonyl)-(3-phenylpropyl)amino]-2-oxopyrrolidin-1-ylmethyl)thiophene-2-carboxamidine_trifluoroacetate;
 - 4-(3-(S)-[(Methanesulfonyl)(naphthalene-2-yl)amino]-2-oxopyrrolidin-1-ylmethyl)thiophene-2-carboxamidine-trifluoroacetate;
 - 4-{3-(S)-[(4,5-Dichlorothiophene-2-sulfonyl)benzylamino]-2-oxopyrrolidin-1-ylmethyl]thiophene-2-carboxamidine,trifluoroacetate;
- 20 oxopyrrolidin-1-ylmethylthiophene-2-carboxamidine-trifluoroacetate; 0
 - 2-[[1-(5-Carbamimidoylthiophene-3-ylmethyl)-2-oxopyrrolidin-3-(S)-ŷl]-(7-__methoxynaphthalene-2-sulfonyl)amino]-N-phenethylacetamide:trifluoroacetate;
- 25_ 2-[[1-(5-Carbamimidoylthiophene-3-ylmethyl)-2-oxopyrrolidin-3-(S)-yl]-(4,5-6 dichlorothiophene-2-sulfonyl)amino]-N-benzylacetamide-trifluoroacetate;
 - 2-[[1-(5-Carbamimidoylthiophene-3-ylmethyl)-2-oxopyrrolidin-3-(S)-yl]-(7-methoxynaphthalene-2-sulfonyl)amino]-N-benzylacetamide trifluoroacetate;
 - 2-[[1-(4-Carbamimidoylthiophene-2-ylmethyl)-2-oxopyrrolidin-3-(S)-yl]-(7-methoxynaphthalene-2-sulfonyl)amino]acetamide trifluoroacetate:
- 2-[[1-(4-Carbamimidoylthjophene-2-ylmethyl)-2-oxopyrrolidin-3-(S)-yl]-(5-chloro-3-methylbenzo[b]thjophene-2-sylfonyl)amino]acetic acid methyl ester;

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70 3

- 4-{3-(S)-[(7-Aminonaphthalene-2-sulfonyl)benzylamino]-2-oxopyrrolidin-1-ylmethyl}thiophene-2-carboxamidine bistrifluoroacetate;
- 4-{3-(\$)-[(7-Aminonaphthalene-2-sulfonyl)methylamino]-2-oxopyrrolidin-1-ylmethyl}thiophene-2-carboxamidine bistrifluoroacetate;
 - 2-[[1-(5-Carbamimidoylthiophene-3-ylmethyl)-2-oxopyrrolidin-3-(S)-yl]-(7-aminonaphthalene-2-sulfonyl)amino]acetamide bistrifluoroacetate;
- 4-[3-(S)-(6-Amino-5-chloro-2-sulfonylamino)-2-oxopyrrolidin-1-ylmethyl]-thiophene-2-carboxamidine trifluoroacetate:
 - 4-{3-(S)-[(6-Amino-5-chloro-naphthalene-2-sulfonyl)methylamino]-2-oxopyrrolidin-1-ylmethyl}thiophene-2-carboxamidine trifluoroacetate;
 - 2-[[1-(5-Carbamimidoylthiophene-3-ylmethyl)-2-oxopyrrolidin-3-(S)-yl]-(6-amino-5-chloronaphthalene-2-sulfonyl)amino]ácetamide trifluoróacetate;
- 4-[3-(S)-(6-Aminonaphthalene-2-sulfonylamino)-2-oxopyrrolidin-1-ylmethyl]-20 thlophene-2-carboxamidine dihydrochloride;
 - 5-[3-(S)-(7-Methoxynaphthalene-2-sulfonylamino)-2-oxopyrrolidin-1-ylmethyl]-thiophene-2-carboxamidine trifluoroacetate; and the substitution of th
- 25 5-{3-(S)-[(7-Methoxynaphthalene-2-sulfonyl)methylamino]-2-oxopyrrolidin-1ylmethyl}thiophene-2-carboxamidine trifluoroacetate;
 - 5-{3-(S)-[(7-Methoxynaphthalene-2-sulfonyl)benzylamino]-2-oxopyrrolidin-1-ylmethyl)thiophene-2-carboxamidine trifluoroacetate;
 - [Amino-(4-{3-(S)-(7-methoxynaphthalene-2-sulfonyl)methylamino]-2-oxopyrrolidin-1-ylmethyl)thiophene-2-yl)methylene]carbamic acid methyl ester trifluoroacetate;
- 4-{3-(\$)-[(7-Methoxynaphthalene-2-sulfonyl)methylamino]-2-oxopyrrolidin-1-ylmethyl)thiophene-2-N-hydroxycarboxamidine trifluoroacetate;

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...i., 4-[3-(S)-(7-Methoxynaphthalene-2-sulfonylamino)-2-oxopyrrolidin-1-ylmethyl]pyridine-2-carboxamidine trifluoroacetate: ad-2-enart aoi n'(1941) amin' 104-{3-(S)-[(7-Methoxynaphthalene-2-sulfonyl)benzylamino]-2-oxopyrrolidin-1vlmethyl)pyridine-2-carboxamidine trifluoroacetate; algo: !tflyrif-mly 4-{3-(S)-[(7-Methoxynaphthalene-2-sulfonyl)methylamino]-2-oxopyrrolidin-1ylmethyl)pyridine-2-carboxamidine trifluoroacetate; 10 4-[3-(S)-(5-Chloro-3-methylbenzo[b]thiophene-2-sulfonylamino)-2oxopyrrolidin-1-ylmethyl]pyridine-2-carboxamidine_trifluoroacetate; -24-{3-(S)-[(5-Chloro-3-methylbenzo[b]thiophene-2-sulfonyl)methylamino]-2coxogyrrolidin-1-ylmethyl)pyridine-2-carboxamidine trifluoroacetate; 15 01 2-{[1-(2-Carbamimidoylpyridine-4-ylmethyl)-2-oxopyrrolidin-3-(S)-yl]-(7methoxynaphthalene-2-sulfonyl)amino}acetamide trifluoroacetate; note: Th. 2-{[1-(2-Carbamimidoyl-pyridine-4-ylmethyl)-2-oxopyrrolidin-3-(\$)-yl]-(7-20 methoxynaphthalene-2-sulfonyl)amino}-N-phenethylacetamide):: trifluoroacetate: to 2000 (7:Methicx respiringlene 2-sultonylain in the oxoby rolidin- to provide 4-{3-(S)-[(7-Methoxynaphthalene-2-sulfonyl)-thiophen-3-ylmethylamino]-2oxopyrrolidin-1-ylmethyl)pyridine-2-carboxamidine trifluoroacetate: 25 5-13-18,-I(T-Methoxynaphthalene 25.55ftchyl)methylan (no) Closcov 4-{3-(S)-[(7-Methoxynaphthalene-2-sulfonyl)thiophen-3-ylmethylamino]-2oxopyrrolidin-1-ylmethyl}thiophene-2-carboxamidine trifluoroacetate; Full-object whether years tradens are alternyt) beneight in the exercise 4-{3-(S)-[(4-(6-Nitro-2-chlorophenoxy)benzenesulfonyl)amino]-2-oxopyrrolidin-1-ylmethyl}thiophene-2-carboxamidine trifluoroacetate; 30 Short districts mitymotice Representation profite medically and continuing 5-{3-(S)-[(7-Methoxynaphthalene-2-sulfonylamino]-2-oxopyrrolidin-1-ylmethyl}furan-2-carboxamidine trifluoroacetate; and

35 4-[3-(S)-(5-Chloro-3-methylbenzo[b]thiophene-2-sulfonylamino)-2-

oxopyrrolidin-1-ylmethyl]furan-2-carboxamidine trifluoroacetate

30

Preferred compounds the group consisting essentially of include:

7-Methoxynaphthalene-2-sulfonic acid {1-[3-(aminoiminomethyl)benzyl]-2-oxopyrrolidin-3-(S)-yl}methyl amide trifluoroacetate;

3'-Methoxy-biphenyl-4-sulfonic acid {1-[3-(aminoiminomethyl)benzyl]-2-oxopyrrolidin-3-(S)-yl}amide trifluoroacetate;

5-Pyrid-2-ylthiophene-2-sulfonic acid {1-[3-(aminoiminomethyl)benzyl]-2-10 oxopyrrolidin-3-(S)-yl)amide trifluoroacetate;

7-Methoxynaphthalene-2-sulfonic acid {1-[3-(aminoiminomethyl)benzyl]-2-oxopyrrolidin-3-(S)-yl}amide trifluoroacetate;

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- 7-Aminonaphthalene-2-sulfonic acid {1-[3-(aminoiminomethyl)benzyl]-2-oxopyrrolidin-3-(S)-yl)amide bistrifluoroacetate;
- 5-Chloro-3-methylbenzo[b]thiophene-2-sulfonic acid {1-[3-(aminoiminomethyl)benzyl]-2-oxopyrrolidin-3-(S)-yl]amide trifluoroacetate; 20. https://doi.org/10.1009/10.10
- 2-[{1-[3-(Aminoiminomethyl)benzyl]-2-oxopyrrolidin-3-(S)-yl}-7methoxynaphthalene-2-sulfonylaminoj-N-phenethylacetamide trifluoroacetate;
- - 2-[{1-[3-(Aminoiminomethyl)benzyl]-2-oxopyrrolidin-3-(S)-yl}-7methoxynaphthalene-2-sülfönylaminoj-Nⁱ(2-pyridin-3-yl-ethyl)acetamide bistriflüöroacetate: himatas som an motivas som an positam
 - 4,5-Dichlorothiophene-2-sulfonic acid (1-[3-(āminoiminomethyl)benzyl]-2-oxo-3(S)-pyrrolidin-3-yl]amide trifluoroacetate;
 - 3'-Methyl-biphenyl-4-sulfonic acid (1'-[3-(aminoiminomethyl)benzyl]-2-35 oxopyrrolidin-3(S)-yl) amide trifluoroacetate;

3-[{1-[3-(Aminoiminomethyl)benzyl]-2-oxopyrrolidin-3(S)-3-yl}-(7methoxynaphthalene-2-sulfonyl)amino]acetamide trifluoroacetate: /-Methorynaphthalene-2-sufferiic acid (1 [3-(amheursideentryhten tyr)-2 7-Methoxy-2-napthalenesulfonic acid (1-[3-(aminoiminomethyl)benzyl]-2-oxo-5 3(S)-pyrrolidin-3-yl}(pyridin-2-ylmethyl)amide trifluoroacetate; 2'-Methoxy urgaeny'-4-sulford: acid 11/3-(aminominomichyl)benz 112 Quinoline-6-sulfonic acid {1-[3-(aminoiminomethyl)benzyl]-2-oxopyrrolidin-3-(S)-yl}amide trifluoroacetate; 5-Pyrid Elythjophene-2-sulfonio acid page (arrinoimenthy) backup. 4-Amino-3-[3-(S)-(7-methoxynaphthalene-2-sulfonylamino)-2-oxopyrrolidin-1yl-methyl]benzamidine dihydrochloride; Z-Maci oxynaphthalene-0-authorid adid (n-i3-(grainoimin mathylthangyli-2) 4-Amino-3-[3-(S)-(7-methoxynaphthalene-2-sulfonyl-methylamino)-2oxopyrrolidin-1-yi-methyl]benzamidine trifluoroacetate: 7-Aminonaphthalene-2-surionic acid (1-j3-(aminoimnom-mythbenoph 31 4-Amino-3-[3-(S)-(4-tert-butylbenzenesulfonylamino)-2-oxopyrrolidin-1-ylmethyl]benzamidine trifluoroacetate; o-Objects of Applicated billifopher a-2-suffering acid (1-43atsie: (4-(Aminojminomethyl)-2-[3-(7-methoxynaphthalene-2-sulfonylamino)-2-20 oxopyrrolidin-1-ylmethyl]phenoxy}acetic acid methyl ester trifluoroacetate: 2-it t-jest Amil a minomethy sensyly-2-oxopyroliais 4: (8)-yty 7-115 2801: 4-[3-(S)-(7-Methoxynaphthalene-2-sulfonylamino)-2-oxopyrrolidin-1-ylmethyl]thiophene-2-carboxamidine trifluoroacetate: 2-[1]-[3-(A) (unoimmomethyl)ben zylf-2-oxopyrcudir-2-(8)-ylf-7-25 4-{3-(S)-[(7-Methoxynaphthalene-2-sulfonyl)methylamino]-2-exopyrrolidin-1ylmethyl}thiophene-2-carboxamidine trifluoroacetate; 2-[] [2-(Aminonimathyl)herzyll-2-oxopyrolidin-3-(5)-yl)-7-2-[[1-(5-Carbamimidoylthiophene-3-ylmethyl)-2-oxopyrrolidin-3-(S)-yl](7methoxynaphthalene-2-sulfonyl)amino]acetamide trifluoroacetate; 30 4-[3-(S)-(5-Chloro-3-methylbenzo[b]thlophene-2-sulfonylamino)-2-oxopyrrolidin-1-ylmethyl]thiophene-2-carboxamidine trifluoroacetate; 4-{3-(\$)-{(5,Chloro-3-methylbenzo[b]thiophene-2-sulfonyl)methylamino]-2-

oxopyrrolidin-1-ylmethyl)thiophene-2-carboxamidine trifluoroacetate;

25

2-[[1-(5-Carbamimidoylthiophene-3-ylmethyl)-2-oxopyrrolldin-3-(S)-yl]-(7-methoxynaphthalene-2-sulfonyl)amino]-N-phenethylacetamide trifluoroacetate;

[Amino-(4-{3-(S)-(7-methoxynaphthalene-2-sulfonyl)methylamino]-2oxopyrrolidin-1-ylmethyl}thiophene-2-yl)methylene]carbamic acid methyl ester trifluoroacetate;

4-{3-(S)-[(6-Amino-5-chloro-naphthalene-2-sulfonyl)methylamino]-2-oxopyrrolidin-1-ylmethyl}thiophene-2-carboxamidine trifluoroacetate;

4-[3-(S)-(6-Amino-5-chloro-2-sulfonylamino)-2-oxopyrrolidin-1-ylmethyl]-thiophene-2-carboxamidine trifluoroacetate;

4-{3-(S)-[(7-Aminonaphthalène-2-sulfonyl)benzylamino]-2-oxopyrrolidin-1-5 ylmethyl}thiophené-2-carbóxamidiné bistrifluoroacetate;

4-[3-(S)-(7-Methoxynaphthalene-2-sulfonylamino)-2-oxopyrrolidin-1-ylmethyl]-pyridine-2-carboxamidine trifluoroacetate;

4-{3-(S)-[(7-Methoxynaphthalene-2-sulfonyl)benzylamino]-2-oxopyrrolidin-1-ylmethyl)pyridine-2-carboxamidine trifluoroacetate;

2-{[1-(2-Carbamimidoyl-pyridine-4-ylmethyl)-2-oxopyrrolidin-3-(S)-yl]-(7-methoxynaphthalene-2-sulfonyl)amino)-N-phenethylacetamide trifluoroacetate;

4-{3-(S)-[(7-Methoxynaphthalene-2-sulfonyl)thiophen-3-ylmethylamino]-2-oxopyrrolidin-1-ylmethyl)thiophene-2-carboxamidine trifluoroacetate; and

4-{3-(S)-[(4-(6-Nitro-2-chlorophenoxy)benzenesulfonyl)amino]-2-oxopyrrolidin-1-ylmethyl}thiophene-2-carboxamidine trifluoroacetate.

and the compounds of formula I may be prepared by the application or apply adaptation of known methods, by which is meant methods used heretofore or 35 juridescribed in the literature; and only as more shirtly decreases as a multiplication of the control of the

Notice (8) - 8. A preparative embodiment according to the invention for preparing a то покупарать всего-sufferyl) an including the ballyngqmonor celeter [Adminol.(4-(3-(2) ป./melhoxy]โลสุXักปอกุX 2-sulfony), กระกylamınoj-2 methyleneicarbainic cold muth; 43-(C)-(C)-American indicensions, introduction of the environment of t carboxemidina fillaureacetate. 4-[3-(3)-(6-AmsRHY chlore 6X ylamino)-2-oxophrolidin-1-ylmethyl thiophene 2 (I) aroundine trifluoroscetate; 5 wherein Ar¹, R, R, R₂₁, X₃, X₄₁, X₅₁, X₅₁, X₆₁, X₆₂, m and n are as defined above, and X₁ and X₁, are hydrogen and X₂ and X₂, taken together are oxo, may be prepared by reacting a compound of formula II $4 \cdot \{2 \cdot (3 \cdot (7 \cdot M_{\odot}) \cdot c) \}$ ynaphlinalane $2 \cdot \sin(any)$ amin or $2 \cdot \exp(y_0)$ oliol $(z_1, z_2, d) \cdot c$ arbyst consider section with a sign of the section of the -(3-(3):[(7-Nethex)nephin in high selection (high selection)) Antipolitical and the City of the Company of the City 10 wherein X3, X4 and m are as defined above, and P1 is alkyl, aralkyl, or aryl, and P2 is (alkyl, aralkyl, for aryl) carbamate, by reductive amination using a cyano(phenyl or heteroaryl)alkylamine of formula III 15 Editor nysomawi Nin(a) Elec -Sold fire starts at the contraction of ธ อเมษารถทาเทิด, ษณิเคิดNC™ 4-(3-45)-1(4 (5-(111) re-2 chrowablenoxy)) X zenosulfanyf) aminaj-2-oxopy r-yimetangh icgnene Pico doxigmotis e Fit saraboerals.

wherein Arth X₆, X₆, and neare as defined above; in an alcoholic solvent such as 20, methanol and an imine reducing reagent such as sodium cyanoborohydride, sodium triacetoxyborohydride or catalytic hydrogenation using for example palladium at a temperature from about 0°C to about 100°C to give the cyclic structure represented by formula IV.

$$X_{3}$$
 X_{4}
 X_{1}
 X_{1}
 X_{1}
 X_{2}
 X_{2}
 X_{2}
 X_{2}
 X_{6}
 X_{6}
 X_{1}
 X_{2}
 X_{3}
 X_{4}
 X_{2}
 X_{2}
 X_{3}
 X_{4}
 X_{2}
 X_{2}
 X_{3}
 X_{4}
 X_{5}
 X_{6}
 X_{6}
 X_{6}
 X_{6}

wherein Ar¹, X₃, X₄, X₆, m and n are as defined above, and X₁ and X₂, are hydrogen, X₂ and X₂, taken together are oxo, and P₂ is (alkyl, aralkyl, or aryl)carbamate. The P₂ group is then removed by the appropriate deblocking procedures known for carbamates such as strong acid, strong base or catalytic hydrogenation to give compounds of formula V.

The state of the s

wherein Ar¹, X₃, (X₄, X₆, X₆, m and n are as defined above, and X₁ and X₂ are thydrogen, and X₂ and X₂, taken together are oxio. The amine of the compound of formula V is then coupled to any of the groups represented by formulae VIa or VIb

The first particles of the form $R_3S(O)_pHalo$ or $R_3H_4NS(O)_pHalo)^{(effect)}$ and $R_3S(O)_pHalo)^{(effect)}$ and $R_3S(O$

୍ଞ ି20 ଜ୍ଞି Where Rg, Rg, and p'āre as defined above, and Halo is a halogen atom such as chloro, using a base such as a trialkylamine in an inert solvent such as

dichloromethane, tetrahydrofuran, ether or acetonitrile at temperatures from about 0°C to about 100°C in the presence or absence of an activating agent such as dimethyl aminopyridine (DMAP) to give compounds of formulae VIIa or VIIb.

wherein Ar1, R3, R4, X3, X4, X6, X6, m, n and p are as defined above, and X, and X₁, are hydrogen, X₂ and X₂, taken together are oxo. Compounds represented by formulae VIIa or VIIb may be converted to the corresponding imidate ester by the use of an alcoholic solvent such as ethanol saturated with hydrogen chloride (gas). The resulting product is then dissolved in an alcoholic solvent such as methanol saturated with ammonia to give compounds of formula I, 15 wherein X₅ and X₅ taken together are =NH. Alternatively, compounds of formula VII can be dissolved in a solution of pyridine containing a tertiary amine base such as triethyl amine saturated with hydrogen sulfide at a temperature from about 0°C to about 60°C. The resulting product is then E dissolved in an organic solvent such as acetone and reacted with an alkyl 20 halide such as methyl jodide at a temperature 0°C to about 80°C. The resulting product is then dissolved in an alcoholic solvent such as methanol and reacted with ammonium acetate to give compounds of formula I, wherein X_s and $X_{s'}$ taken together are =NH. diV -

25 When X_1 and X_2 and X_2 are independently selected from hydrogen, optionally substituted alkyl; optionally substituted aryl, optionally substituted aralkyl, optionally substituted heteroaryl, optionally substituted heteroaralkyl or hydroxyalkyl, compounds of formula I may be prepared starting with may be prepared by reacting a compound of formula VIII. Should

$$\begin{array}{c} P_1O \\ X_3 \\ X_2 \\ O \end{array} \begin{array}{c} X_3 \\ X_4 \\ P_2 \\ (VIII) \end{array}$$

wherein X₃, X₄ and m are as defined above, X₂ is hydrogen, optionally 5 substituted alkyl, optionally substituted aryl, optionally substituted aralkyl, optionally substituted heteroaryl, optionally substituted heteroaralkyl, carboxyalkyl, alkoxycarbonylalkyl or hydroxyalkyl, and P1 is alkyl, aralkyl, or aryl, and P2 is (alkyl, aralkyl, or aryl)carbamate, with a compound of formula III as defined above in an analogous fashion to the reaction of the compound of formula II with a compound of formula III. The product of the reaction of compounds of formulae VIII and III yields a compound of formula IV wherein Ar, X_3 , X_4 , X_6 , X_6 , m and n are as defined above, and X_1 and X_1 , taken together are oxo, one X_2 and X_2 , is hydrogen and the other of X_2 and X_2 is hydrogen, optionally substituted alkyl, optionally substituted aryl, optionally substituted 15 aralkyl, optionally substituted heteroaryl, optionally substituted heteroaralkyl or hydroxyalkyl, and P2 is an (alkyl, aralkyl or aryl)carbamate. That compound of formula IV may then be converted to a compound of formula V and then on to compounds of formulae VIIa and VIIb wherein Ar^1 , R_3 , R_4 , X_3 , X_4 , X_6 , X_6 , R_6 and p are as defined above, and X_1 and X_2 are oxo, and one X_2 and X_2 , is hydrogen and the other of X2 and X2 is hydrogen, optionally substituted alkyl, 20 optionally substituted aryl, optionally substituted aralkyl, optionally substituted heteroaryl, optionally substituted heteroaralkyl, or hydroxyalkyl in an analogous procedure to that given for the conversion of a compound of formula IV to a compound of formula V which is then converted to compounds of 25 formulae VIIa or VIIb.

Alternatively, compounds of formula V and formula IV may be converted to a compounds of formula I as follows. Compounds of formulae IV or V are treated with an alcoholic solvent such as ethanol saturated with HOI. The resulting product is then treated with an alcoholic solvent such as methanol saturated with ammonia to give respectively a compound of formula IX or X

 X_{i} and it connects and X_{i} X_{i}

subgituted the contour say substituted and continuing the stitutes optionsity substituted heteroaryl, cononally substituted(XI)teroaralkyr. ec boxyalket, alkoxycarbonylalkył or tydromialkył, and Pij is alkył, ar alkył, o. to 5.5 compound of formula IX may then be converted to a compound of formula X by to an appropriate deblocking procedure described above did compound of rissent formula X may then be dissolved in an organic solvent such as ethanol or allego! adimethylformamide and compounds of formulae Viavor Vibrare added at a nego: temperature from about 0°C to about 100°C in the presence of absence of an 5:10 He activating reagent such as DMAP with a sulfonviction to give compounds aralkyl, updonally subsituted betarostyl, otifisiumolyde betaresarencyl or hydroxyawyt, and Paits an (alky , arclicytionaryhoarbamate. That compound of and the thing Alternatively a compound of formula I may be prepared starting a to a compound of formula XI. in sety, and one ally enterned to absolute the 15, and set defined above, and X, and X, are brokened and the Xg and Ag. 21 hydrogen and the other of X₂ and X₂ is hydrogen, optionally subcitivited any option: By substituted aryl, Haxasiy, abstituted aralkyr, optionally substituted neverity of ambedding abopt with to it regrees of servers and YardiNe V 32m or to bruce the a of M (XI)/ is AHV estumble

wherein X₁, X₁, X₂, X₃, X₄, X₆, X₆, m and P₂ are as defined above. A

20 compound of formula XI is dissolved in an inert organic solvent such as
tetrahydrofuran at a temperature from about 78°C to about 25°C. To that
solution is added a strong base such as sodium hydride. Ithium used to
hexamethyldisilylazide, or lithium disopropyl amine; followed by the addition of
a compound of formula XII compound of strong discourses

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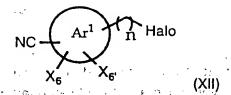
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James And Francis No.



wherein X₆, X₆ and n are as defined above, and halo is a halogen atom such as chloro bromo or lodo to give a compound of formula IV which is then converted to a compound of formula I as described above.

A compound of formula I in which R is other than hydrogen may be prepared starting with compounds of formulae VIIa or VIIb. Compounds of formulae VIIa or VIIb may be dissolved in an inert organic solvent such as tetrahydrofuran, dioxane, or dimethyl formamide at a temperature of about 0°C to about 100°C. To the resulting solution is added a base such as sodium hydride or potassium carbonate and a compound of formula XIII.

> Gillian to on a soft as the R-Hálo

wherein R is as defined above except for hydrogen and halo is a halogen such as chloro or bromo. The product of this preparation is a compound of formula THE POST OF THE STATE OF THE ST

of thems and to the entract of the tagent and fam better in the low same number uni an Xasa ya X41 Tana kasina di mengan Jan. กระทำสาราช และ คำสาราช สูโลร์ตา CXIV) Cook with VIX) multiple where X, and Suute natiogen.

> wherein R₁₁ X₁, X₁, X X₂, X₃, X₄, X₅, m and n are as defined above, and R is optionally substituted alkyl, optionally substituted aralkyl, optionally substituted heteroaralkyl or hydroxyalkyl. A compounds of formula XIV is then converted to

a compound of formula I as described above, that contains a -C(=NH)NH, moiety.

Alternatively, a compound of formula XIV may be treated with an alcoholic solvent such as ethanol saturated with HCl. The resulting product is 5 then treated with an alcoholic solvent such as methanol saturated with an alkylamine, nydrazine or alkoxyamine to give a compound of formula I wherein Ted R, R, X, X, X, X, X, X, X, X, m and n are as defined above, X, and X, taken together are =NR_s, R₂ and R_s are independently hydrogen or alkyl, or when one

of R₂ or R₅ is hydrogen, then the of R₂ or R₅ may be alkoxy or amino. A compound of the formula I wherein X, and X₅ taken together are =NR₅ and R₅ is nitro may be prepared by standard nitrating reactions on a compound of

15 A compounds of formula I wherein X₅ and X₅ taken together are =NR₅ and R₅ is R₆O₂C, R₆CO or cyano may be prepared from compounds of formula I wherein X_s and X_s taken together are =NR_s wherein R_s is hydrogen. For example, the amidine species is treated with an alkyl chloroformate in an appropriate solvent such as methylene chloride or dimethyl formamide in the presence of a base such as a trialkylamine to give a compound of formula I wherein Rs is ReO2C: Similarly, the amidine may be treated with an acylating species such as an acyl chloride in the presence of a base such as trialkylamine to give compounds of formula I wherein Rs is RsOC. Alternatively, compounds wherein R_s is cyano may be prepared by treatment of the amidine with cyanogen bromide and a trialkyl amine in an appropriate an alcoholic A compound of formula I wherein X_s and X_s are hydrogen may be solvent.

prepared by reduction of compounds of formulae VIIa, VIIb or XIV using hydrogenation in an appropriate solvent such as methanol in the presence of a catalyst such as rhodium on alumina. This transformation may also be achieved using a hydride reagent such as diisobutyl aluminum hydride to give a compound of formula I wherein X_s and X_s are hydrogen.

The compounds of the present invention are useful in the form of the free base or acid or in the form of a pharmaceutically acceptable salt thereof. All of ord and forms are within the scope of the invention.

Where the compound of the present invention is substituted with a basic moiety, acid addition salts are formed and are simply a more convenient form for use; and in practice, use of the salt form inherently amounts to use of the free base form. The acids which can be used to prepare the acid addition salts include preferably those which produce, when combined with the free base, pharmaceutically acceptable salts, that is, salts whose anions are non-toxic to the patient in pharmaceutical doses of the salts, so that the beneficial inhibitory effects on the activity of Factor Xa inherent in the free base are not vitiated by 10 side effects ascribable to the anions. Although pharmaceutically acceptable salts of said basic compounds are preferred, all acid addition salts are useful as sources of the free base form even if the particular salt, per se, is desired code conly as an intermediate product as, for example, when the salt is formed only sent a for purposes of purification, and identification, or when it is used as ...15, es intermediate in preparing a pharmaceutically acceptable salt by ion exchange procedures. Pharmaceutically acceptable salts within the scope of the invention are those derived from the following acids: mineral acids such as hydrochloric acid, sulfuric acid, phosphoric acid and sulfamic acid; and organic acids such as acetic acid, citric acid, lactic acid, fartaric acid, malonic acid, 20 methanesufonic acid, ethanesulfonic acid, benzenesulfonic acid, ptoluenesulfonic acid, cyclohexylsulfamic acid, quinic acid, and the like. The corresponding acid addition salts comprise the following: hydrohalides, e.g. hydrochloridesand hydrobromide, sulfate, phosphate, nitrate, sulfamate, anacetate, citrate l'actate, tartarate, malonate, oxalate, salicylate, propionate, succinate, fumarate, maleate, methylene-bis-B-hydroxynaphthoates, ad the gentisates, mesylates, isethionates and di-p-toluoyllartratesmethanesulfonate, ethanesulfonate, benzenesulfonate, p-toluenesulfonate, cyclohexylsulfamate and quinate, respectively.

30 and addition salts of the compounds of this invention are prepared by reaction of the free base with the appropriate acid, by the application of adaptation of known methods. For example, the acid addition salts of the compounds of this invention are prepared either by dissolving the free base in aqueous or aqueous alcohol as solution or other sultable solvents containing the appropriate acid and isolating the salt by evaporating the solution, or by reacting the free base and acid in an

interest of a mipotence of the present investigation may be obtained in

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organic solvent, in which case the salt separates directly or can be obtained by Witere the compound of the solution pre-nothing entropy and the compound of the solution of th

molety, acid addition saits are formed and are simply a more convenient form The compounds of this invention may be regenerated from the acid addition salts by the application or adaptation of known methods? For example, ... parent compounds of the invention can be regenerated from their acid addition salts by treatment with an alkali, e.g. aqueous sodium bicarbonate solution or the Latient in pharmaceut act a line of theorems along the charmageurgupa

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effects on the activity of Egotor (to in latent in the way base his net vituated to Where the compound of the invention is substituted with an acidic mojety, base addition salts may be formed and are simply a more convenient form for use; and in practice, use of the salt form inherently amounts to use of the free acid form. The bases which can be used to prepare the base addition salts include preferably those which produce; when combined with the free acid, pharmaceutically acceptable salts; that is; salts; whose cations are nontoxic to the animal organism in pharmaceutical doses of the salts; so that the beneficial inhibitory effects on the activity of Factor Xa inherent in the free acid are not vitiated by side effects ascribable to the cations: Pharmaceutically acceptable salts, including for example alkali and alkaline earth metal salts. within the scope of the invention are those derived from the following bases: sodium hydride, sodium hydroxide, potassium hydroxide, calcium hydroxide, aluminum, hydroxide, lithium, hydroxide, magnesium, hydroxide, zinc hydroxide, ammonia, ethylenediamine, N-methyl-glucamine, lysine, arginine, ornithine. choline, N,N'-dibenzylethylenediamine, chloroprocaine; diethanolamine, procaine, N-benzylphenethylamine, diethylamine, piperazine, and co tris(hydroxymethyl)aminomethane, tetramethylammonium hydroxide; and the like. Internative enable of Chambitus area of the enables enables expension of the enables ena

Metal salts of compounds of the present invention may be obtained by contacting a hydride, hydroxide, carbonate or similar reactive compound of the chosen metal in an aqueous or organic solvent with the free acid form of the compound. The aqueous solvent employed may be water or it may be a mixture of water with an organic solvent, preferably an alcohol such as methanol or ethanol, a ketone such as acetone, an aliphatic ether such as tetrahydrofuran, or an ester such as ethyl acetate. Such reactions are normally conducted at ambient temperature but they may, if desired, be conducted with heating.

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Amine salts of compounds of the present invention may be obtained by contacting an amine in an aqueous or organic solvent with the free acid form of the compound. Suitable aqueous solvents include water and mixtures of water with alcohols such as methanol or ethanol, ethers such as tetrahydrofuran, nitriles such as acetonitrile, or ketones such as acetone. Amino acid salts may be similarly prepared.

The base addition salts of the compounds of this invention can be regenerated from the salts by the application of adaptation of known methods. For example, parent compounds of the invention can be regenerated from their base addition salts by treatment with an acid, e.g. hydrochloric acid.

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Salt forms according to invention also include compounds having a quarternarized nitrogen. The quarternarized salts are formed by methods such as by alkylation of a sp³ or sp² hybridized nitrogen in the compounds.

As will be self-evident to those skilled in the art, some of the compounds of this invention do not form stable salts. However, acid addition salts are most likely to be formed by compounds of this invention having a nitrogen-containing heteroaryl group and/or wherein the compounds contain an amino group as a substituent. Preferable acid addition salts of the compounds of the invention are those wherein there is not an acid-labile group.

As well as being useful in themselves as active compounds, salts of compounds of the invention are useful for the purification of the purification of the purification of the selectompounds for example by exploitation of the solubility differences between the falls and the parent compounds, salts of the solubility differences between the falls and the parent compounds, salts of the solubility differences between the salts and the parent compounds, salts of the salts and the parent compounds and are the parent compounds are the parent compounds are the parent compounds are the parent compounds.

These asymmetric centers may independently be in either the H or S on configuration. It will also be apparent to those skilled in the art that certain compounds of formula i may exhibit geometrical isomers include the cis and trans forms of compounds of the invention having alkenyl or diazenyl (azo) moieties. The present invention comprises the

to notice of viSuch isomers can be separated from their mixtures, by the application or to notice of vision of known methods; for example chromatographic techniques and sales. It is appropriate isomers of their intermediates, for example by the application or notices such as accondition, nierable bedings by the appropriate isomethods; described herein, intermediatey prepared.

The starting materials and intermediates are prepared by the application or adaptation of known methods; for example methods as described in the ...by. 10 n. Reference Examples or their obylous chemical equivalents standard For example, parent compounds of the invention can be regenerated from their Dias The present invention is further exemplified but not limited by the following examples which illustrate the preparation of the compounds Sait forms according to invention at noitheynly of pripropagation of quarternarized nitrogen. The quarternarized salts are formed by methods 1.71 - 1.71 and the nuclear magnetic resonance spectra (NMR) the chemical shifts are expressed in ppm relative to tetramethylsilane. Abbreviations have the supposed following significance: s=singlet; d=doublet; t=triplet; m=multiplet; dd=doublet is in sign of doublets; ddd=doublet of doublets of doublets; dt=doublet of triplets. 20 b=broad, bs=broad singlet, q=quartet, AB=AB patternino sci of viewi :3. containing heteroard group and/or wherein the compounds contain an arrive of group as a substituent. Professible acid addition sales of LELOMAXE of a continuent Naphthalene-2-sulfonic acid {1-[3-(aminoiminomethyl)benzyl]-2-oxopyrrolidin-3-(S)-vl}amide trifluoroacetate.

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A. Boc-L-Asp(H)-OBD, out not luterup era notionatal ent to abring not

Boc-L-Asp-OBD, (15,g, 46.4 mmol) is dissolved in 50 mL of THE and cooled to

-10°C; The solution is treated with N-methylmorpholine (4.9 g) 48.7 mmol) and

stirred for 5 minutes. To the solution is added dropwise isobutyl chloroformate

(6.3 g, 46.4 mmol). After the addition is completed, the solution is stirred for 1

minute, then filtered through a pad of Celite. The collected solution is cooled to

-10°C; To the solution is added sodium borohydride; (2.63 g; 70 mmol)

predissolved in 50 mL of water of The solution is stirred for 2 minutes of the

solution is poured into a separatory funnel and diluted with 800 mL of EtOAc.

The organic layer is washed with water and saturated NaCl., The organic layer

is dried over MgSO4, filtered and concentrated. The resulting residue is added

to a solution of oxally chloride (30 mL of a 2 M solution in CH₂Cl₂: 60 mmol),

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and methyl sulfoxide (7.25 g, 92.8 mmol) in 250 mL of CH₂Cl₂ at -78°C. The reaction mixture is stirred at -78°C for 40 minutes, then triethylamine (14 g, 140 mmol) is added. The reaction mixture is stirred at -78°C for 1 hour and then is stirred at room temperature for 30 minutes. The solution is poured into 200 mL of a 20% citric acid/water solution. The resulting mixture is poured into a separatory funnel and the layers are separated. The organic layer is washed with water and saturated NaCl. The organic layer is dried over MgSO4, filtered and concentrated. The residue is purified by column chromatography eluting with a gradient of 10% EtOAc/hexanes to 30% EtOAc/hexanes. The product aldehyde (12 g, 39 mmol) is obtained as an oil adaption of the second 'H NMR (CDCI₃, 300 MHz) δ 9.68 (s, 1H), 7.32 (m, 4H), 5.42 (bs, 1H), 5.16 (s, 2H), 4.62 (m, 2H), 3.05 (ddd, 2H), 1.40 (s, 9H),

HICKER DOCESO-C, BOOKMERZ) & BLOCK THY, BLOCK THY, BIOR B. [1-(3-Cyanobenzyl)-2-oxopyrrolidin-3-(S)-yl]carbamic acid tert-butyl ester. To a solution of Boc-L-Asp(H)-OBn (13.5 g, 44 mmol) dissolved in 75 mL of methanol is added m-cyanobenzylamine hydrochloride (7.4 g, 44 mmol) and triethylamine (4.7 g, 46 mmol). The solution is stirred for 30 minutes. After this time, a solution of sodium cyanoborohydride (3 g, 48.4 mmol) and zinc chloride (3.3 g, 24.2 mmol) in 30 mL of MeOH is added. The mixture is stirred for an additional 2 hours. After this time, 20 mL of 1 N NaOH and 100 mL of water is added, and the resulting mixture is concentrated. The residue is treated with 100 mL of water and 800 mL of EtOAc. The solution is filtered through a pad of Celite, poured into a separatory funnel and the layers are separated. The organic layer is washed with 1 N HCl, 10% Na2CO3 and saturated NaCl. The 25 organic layer is dried over MgSO₄, filtered and concentrated. The residue is purified by column chromatography eluting with a gradient of 20% 4A EtOAc/CH₂Cl₂ to 40% EtOAc/CH₂Cl₂ to give the title compound (9.1 g, 29 mmol) CHECKING COLD 1% TEA). The appropriate fractions aubilos elithed a sa 1H NMR (CDCI₃, 300 MHz), δ, 7.55 (m, 4H), 5.18 (bs. 1H), 4.47 (AB, 2H), 4.18 ... 30 (dd, 1H), 3.21 (m, 2H), 2.60 (m, 1H), 1.88 (m; 1H), 1.42 (s/9H)

.C. 3-(3-(S)-Amino-2-oxopyrrolidin-1-ylmethyl)benzonitrile hydrochloride. To-a solution of [1-(3-cyanobenzyl)-2-oxopyrrolidin-3-(S)-yl]carbamic acid tertbutyl ester (9.1 g, 29 mmol) in 150 mL of EtOAc at 0°C is bubbled HCl gas for 35 10 minutes. After this time, the solution is stirred for 4 hours. The solution is then concentrated to give the title compound (7.3 g, 29 mmol) as a white solid.

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H NMR (DMSO-d_s, 300 MHz) δ 8.71 (bs, 3H), 7.85 (m, 2H), 7.70 (m, 2H), 4.58 (m, 2H), 4.13 (m, 1H), 3.32 (m, 2H), 2.44 (m, 1H), 2.18 (m, 1H).

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3-(3-(S)-Amino-2-oxopyrrolidin-1-ylmethyl)benzonitrile hydrochloride (0.4 g, 1.5 mmol) is suspended in 10 mL of CH₂Cl₂. To the solution is added with critical viriethylamine (0.49 g, 4.8 mmol) followed by 2-naphthalene sulfonyl chloride (0.49 g, 1.8 mmol). After stirring for 2 hours, the solution is diluted with CH₂Cl₂.

The solution is washed with TN HCl. 10% Na₂CO₃ and saturated NaCl. The organic layer is dried over MgSO₄, filtered and concentrated. The residue is triturated with ether to give the title compound (0.46 g, 1.13 mmol) as a solid. HNMR (DMSO-d₆, 300 MHz) δ 8.56 (d, 1H), 8.32 (d, 1H), 8.20 (m, 3H), 8.09 (m, 1H), 7.93 (d, 1H), 7.74 (m, 3H), 7.48 (d, 2H), 4.38 (AB, 2H), 4.17 (m, 1H), 15 m 3.05 (m, 2H), 2.02 (m, 1H), 1.57 (m, 1H)

ender to a Eas Naphthalene-2-súltonic สีcid (รี-โ3-(alminoimihomethyl)benzylj-2-อการใกร อัxòpyrrólidin-3-(S)-yl)amide trifluòròacetate เอเลยา to noture a เลย

mismanol is uitded m-chanopentylamine hydrochlorida (7.4 g, 44 mmc/ 🛫 d

Naphthalene-2-sulfonic acid [1-(3-cyanobenzyl)-2-oxopyrrolidin-3-(S)-yl]amide (0.46 g, 1.13 mmol) is dissolved in 50 mL of ethanol. The solution is cooled to 0°C and HCl gas is bubbled through the solution for 10 minutes. The ice bath is removed and the reaction mixture is stirred at room temperature for 6 hours.

After this time, the solution is cooled to 0°C and ammonia gas is bubbled through the solution for 10 minutes. The reaction mixture is stirred for 24 hours. After this time, the solution is cooled to 0°C and ammonia gas is bubbled through the solution for 10 minutes. The reaction mixture is stirred for 24 hours. After this time, the solution is concentrated. The residue is purified by RP-HPLC eluting with a gradient of 10% CH₃CN/H₂O (0.1% TFA) to 60%

HPLC eluting with a gradient of 10% CH₃CN/H₂O (0.1% TFA) to 60% CH₃CN/H₂O (0.1% TFA). The appropriate fractions are lyophilized to give the title compound (0.33 g, 0.61 mmol) as a solid. (0.00 g, 0.00) (1.41 H)

30 ¹H NMR (DMSO-d₈, 300 MHz) 8 9:30 (bs, 2H), 9:14 (bs, 2H), 8:50 (s, 1H), 8:28 (d, 1H), 8:13 (m, 3H), 8:04 (d, 1H), 7:91 (d, 1H), 7:80 (m, 3H), 7:62 (d, 2H), 4:42 (AB; 2H), 4:18 (m, 1H), 3:10 (m, 2H); 2:00 (m, 1H); 1:57 (m, 1H); FAB; MS,

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CAMPLE

<u>Dibenzofuran-2-sulfonic acid {1-[3-(aminoiminomethyl)benzyl]-5-oxopyrrolidin-3-yl}amide trifluoroacetate.</u>

A. Boc-Asp(OBn)-H.

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- The title compound is prepared as in EXAMPLE 1, Part A, using Boc-Asp(OBn)-OH in place of Boc-L-Asp-OBn.

 1H NMR (CDCl₃, 300 MHz) δ 9.67 (s, 1H), 7.32 (m, 5H), 5.60 (bs, 1H), 5.12 (AB, 2H), 4.40 (m, 1H), 3.94 (AB, 1H), 3.72 (AB, 1H), 1.41 (ŝ, 9H).
- 10 B. [1-(3-Cyanobenzyl)-5-oxopyrrolidin-3-yl]carbamic acid ten-butyl ester.

 The title compound is prepared as in EXAMPLE 1, Part Brusing Boc-Asp(OBn)-H in place of Boc-Asp(H)-OBn. (2007) (
 - C. 3-(3-Amino-5-oxopyrrolidin-1-ylmethyl)benzonitrile hydrochloride.

 The title compound is prepared as in EXAMPLE 1, Part C using [1-(3-cyanobenzyl)-5-oxopyrrolidin-3-yl]carbamic acid tert-butyl ester in place of [1-(3-cyanobenzyl)-2-oxopyrrolidin-3-(S)-yl]carbamic acid tert-butyl ester.

 1H NMR (DMSO-d₆:300 MHz) δ 8.5 (bs, 3H), 7.72 (m, 2H), 7.61 (m, 1H), 7.55 (m, 1H), 4.46 (AB, 2H); 3.89-(m, 1H), 3.57 (q, 1H), 3.30 (dd, 1H), 2.78 (AB, 1H), 2.42 (AB, 1H).
 - 25 Ja Des Dibenzofuran-2-sulfonic acid [1-(3-cyanobenzyl)-5-oxopyrrolidin-3-yl]amide.

The title compound is prepared from 3-(3-amino-5-oxopyrrolidin-1-ylmethyl)benzonitrile hydrochloride as in EXAMPLE in Part Dusing 2-dibenzofuransulfonyl chloride in place of 2-naphthalene sulfonyl chloride. The crude product is purified by column chromatography in a gradient of CH₂Cl₂ to 5% MeOH/CH₂Cl₂. But the substitution of the crude product is purified by column chromatography in a gradient of CH₂Cl₂ to 5% MeOH/CH₂Cl₂. But the substitution of the crude product is purified by column chromatography in a gradient of CH₂Cl₂ to 5% MeOH/CH₂Cl₂. But the substitution of the crude product is purified by column chromatography in a gradient of CH₂Cl₂ to 5% MeOH/CH₂Cl₂. But the substitution of the crude product is purified by column chromatography in a gradient of CH₂Cl₂ to 5% MeOH/CH₂Cl₂. But the substitution of the crude product is purified by column chromatography in a gradient of CH₂Cl₂ to 5% MeOH/CH₂Cl₂. But the substitution of the crude product is purified by column chromatography in a gradient of CH₂Cl₂ to 5% MeOH/CH₂Cl₂. But the substitution of the crude product is purified by column chromatography in a gradient of CH₂Cl₂ to 5% MeOH/CH₂Cl₂. But the substitution of the crude product is purified by column chromatography in a gradient of CH₂Cl₂ to 5% MeOH/CH₂Cl₂. But the substitution of the crude product is purified by column chromatography in a gradient of CH₂Cl₂ to 5% MeOH/CH₂Cl₂. But the substitution of the crude product is purified by column chromatography in a gradient of CH₂Cl₂ to 5% MeOH/CH₂Cl₂. But the substitution of the crude product is purified by column chromatography in a gradient of CH₂Cl₂ to 5% MeOH/CH₂Cl₂. But the substitution of the crude product is purified by column chromatography in a gradient of CH₂Cl₂ to 5% MeOH/CH₂Cl₂. But the substitution of the crude product is purified by column chromatography in a gradient of CH₂Cl₂ to 5% MeOH/CH₂Cl₂ to 5% MeOH/CH₂Cl₂ to 5% MeOH/CH₂Cl₂

E. Dibenzofuran-2-sulfonic acid (1-[3-(aminoiminomethyl)benzyl]-5-oxopyrrolidin-3-yl)amide trifluoroacetate.

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Hydrogen sulfide gas is bubbled through a solution of dibenzofuran-2-sulfonic 150 T. W.J. acid [1-(3-cyanobenzyl)-5-oxopyrrolidin-3-yl]amide (0.44 g; 0.99 mmol) in 10 mL of 10:1 pyridine/triethylamine. After stirring the pale green solution for a period of 18 hours, the reaction mixture is concentrated in vacuo. The residue The is diluted in EtOAc and 0.5 N HCl solutions: The layers are separated and the organic phase is washed with saturated NaClA-The organic layer is dried over anhydrous MgSO4 filtered and concentrated to give crude thio amide. To a solution of thioamide in 20 mL of acetone is added methyl iodide (2 mL, 32 mmol). The resulting mixture is heated at reflux for 1 hour, allowed to cool to 10 room temperature and concentrated in vacuo to provide the crude thioimidate tot place hydrolodide: To a solution of thiolmidate hydrolodide in 20 mill of MeOH is added ammonium acetate (0.3 g, 3.89 mmol). The resulting mixture is heated at reflux for 3.5 hours, allowed to cool to room temperature and concentrated in SELS (HI vacuo to provide the crude amidine salt. The crude product is purified by RP-HPLC eluting in a gradient of 10% CH₃CN/H₂O (0.1% TFA) to 60% CH₃CN/H₂O (0.1% TFA) and the appropriate product fractions are lyophilized to provide the title compound (0.21 g. 0.36 mmol) as a white solid-c-prime 65-6 0 ¹H NMR (DMSO-d₆, 300 MHz) δ 9.29 (s, 4H), 8.64 (s; 1H), 8.24 (d, 1H), 8.13 (d, 20 (dd, 1H), 3,08 (dd, 1H), 2,46 (dd, 1H); 2.13 (dd, 1H) (FAB MS) [M+H]+463 Elemental analysis calculated with 2.3 mole of H₂O: C=50:50%, H=4.51%. N=9.06%; found C=50.49%, H=3.66%, N=8.61% IS . (A) 3K F (HI , m) 2.42 (A3, 1H)

EXAMPLE 3

25 Toluene-4-sulfonic acid (1-[3-(aminoiminomethyl)benzyl]-2-oxopyrrolidin-3-(S)-yl)amide trifluoroacetate.

The title compound is prepared as in EXAMPLE 1). Part D using toluene

- 30 g sulfonylichloride in place of 2-naphthalene sulfonyl chloride on above C3 TH NMR (DMSO-d₆, 300 MHz) d 8.08 (d, 1H), 7.78 (m),3H),47.62 (s; 1H), 7.51 (d,2H), 7;33 (d, 2H), 4.40 (AB; 2H), 4.05 (m, 1H), 3:05 (m),2H), 2:36 (s; 3H), c = 1.97 (m, 1H), 1.57 (m, 1H), 3:05 (m), 2H) (H) m) 25.3 (H) m) 24.5 (H)
 - 35 B. Toluene-4-sulfonic acid (1-[3-(aminoiminomethyl)benzyl]-2-oxopyrrolidin-3-(S)-yl]amide trifluoroacetate. (3) tries simple trifluoroacetate. (3) tries simple trifluoroacetate. (4) tries simple trifluoroacetate.

The title compound is prepared as in EXAMPLE 1, Part E using toluene-4sulfonic acid [1-[3-(cyanobenzyl)-2-oxopyrrolidin-3-(S)-yllamide as the starting

¹H NMR (DMSO-d_s, 300 MHz) d 9.27 (bs, 2H), 9.10 (bs, 2H), 8.03 (d, 1H), 5 7.79 (d, 2H), 7.68 (m, 1H), 7.59 (m, 4H), 7.40 (d, 2H), 4.44 (AB, 2H), 4.12 (m,

1H), 3.08 (m, 1H), 2.38 (s, 3H), 2.04 (m, 1H), 1.58, (m, 1H). FAB MS. [M+H]+=355. Elemental analysis calculated with 1.25 mole of H₂O: C=48.23%, H=4.59%, N=10.39%, found C=48.15%, H=4.59%, N=10.39%.

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EXAMPLE 4m materials of 1 later with the 10 3.4-Dihvdro-1H-isoquinoline-2-sulfonic acid [1-[3-(amlnoiminomethyl)benzyl]-2-oxopyrrolidin-3-(S)-vl}amide trifluoroacetate.

A: 3.4-Dihydro-1H-isoquinoline-2-sulfonic acid [1-(3-cyanobenzyl)-2-

15 J (oxopyrrolidin-3-(S)-yl]amidestword between actions in 197

0.36 mmol) as a solid.

A 1 M solution of sulfuryl chloride (14.1 mL, 14.1 mmol) in CH₂Cl₂ is cooled to 0°C. To the solution is added triethylamine (0.71 g, 7.1 mmol) dropwise. 1,2,3,4-Tetrahydroisoquinoline (0.94 g, 7.1 mmol) is then added dropwise. The

ice bath is removed and the solution is stirred for 2 hours. The solution is

- 20 and diluted with CH2Cl2 and poured into an ice bath. The layers are separated: The organic layer is washed with 1 N HCl and saturated NaCl. The organic layer is dried over MgSO4, filtered and concentrated. To the crude residue dissolved in 10 mL of CH₂Cl₂ is added 3-(3-(S)-amino-2-oxopyrrolidin-1ylmethyl)benzonitrile hydrochloride (0.5 g, 2 mmol). Triethylamine (0.4 g, 4
- mmol) is added and the mixture is stirred for 16 hours. The reaction mixture is 11) SIT diluted with EtOAc and washed with 1 N HOI, 10% Na CO, and saturated NaCl. The residue is purified by column chromatography eluting with a gradient of 10% EtOAc/CH₂Cl₂ to 15% EtOAc/CH₂Cl₂ to give the title compound (0.15 a. E. 6. Phopheographenyi-i-ulfonyi onlowle
 - 30 : 1H-NMR (CDCI3)300 MHz) δ 7.62 (m, 1H), 7.62 (s, 1H), 7.58 (d, 2H), 7.18 (m, 4H), 7:09 (m; 2H), 5:10 (bs; 1H), 4:46 (AB, 2H), 4:08 (m, 1H), 3:65 (m, 2H), 3:22 (m, 2H), 3.02 (m, 2H), 2.61 (m, 1H), 2.05 (m, 1H). FAB MS, [M+H] = 411. infinitel and then is transferred via cannula to a solution of condensed the

ு மி<mark>த்சிரு 4-Dihydro-1H-isoquinoline-2-sulfonic acid (1-13</mark>- ⁰⁺) செடி விச்சும்

(aminoiminomethyl)benzyll-2-oxopyrrollidin-3-(S)-yl)amide trifluoroacetate. The title compound is prepared as described in EXAMPLE 1. Part E using blackleriunate as a solid. The solid is suspended to 10 mL of hexanes don't

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EXAMPLE 5

10 <u>3'-Methoxy-biphenyl-4-sulfonic acid {1-[3-(aminoiminomethyl)benzyl]-2- in oxopyrrolidin-3-(S)-yl}amide trifluoroacetate ninnosi-Hi-onbyriid-A.E.</u>

A. 3'-Methoxy-biphenyl-4-bromide.

- 3-Bromoanisole (3.5 g, 18.7 mmol) is dissolved in 40 mL of THF and cooled to -78°C. To the solution is added dropwise a 2.5 M solution of n-butyllithium in hexanes (7.5 mL, 18.7 mmol). After 10 minutes, a solution of zinc chloride (20 mL, 19.6 mmol) in ether is added and the cooling bath is removed. The reaction mixture is stirred at room temperature for 2 hours. After this time, a solution of 4-jodobromobenzene (5.6 g, 19.6 mmol) and Pd(Ph3P)4 (1.1 g, 1
- 20 mmgl) in 10 mL of THE is added to the reaction flask. The solution is stirred 2 hours, poured into 100 mL of water and extracted with EtOAc. The organic gaper is washed with water and saturated NaCl. The organic layer is dried over MgSO4 filtered and concentrated. The crude residue is purified by column chromatography eluting with 10% CH2Cl/hexanes to 20% CH2Cl/hexanes to 25 give the title compound (1.5 g, 5.7 mmol) as a solid to be be a flower of the title compound (1.5 g, 5.7 mmol) as a solid to be be a flower of the title compound (1.5 g, 5.7 mmol) as a solid to be be a flower of the title compound (1.5 g, 5.7 mmol) as a solid to be be a flower of the title compound (1.5 g, 5.7 mmol) as a solid to be be a flower of the title compound (1.5 g, 5.7 mmol) as a solid to be be a flower of the title compound (1.5 g, 5.7 mmol) as a solid to be be a flower of the title compound (1.5 g, 5.7 mmol) as a solid to be be a flower of the title compound (1.5 g, 5.7 mmol) as a solid to be be a flower of the title compound (1.5 g, 5.7 mmol) as a solid to be be a flower of the title compound (1.5 g, 5.7 mmol) as a solid to be be a flower of the title compound (1.5 g, 5.7 mmol) as a solid to be be a flower of the title compound (1.5 g, 5.7 mmol) as a solid to be be a flower of the title compound (1.5 g, 5.7 mmol) as a solid to be be a flower of the title compound (1.5 g, 5.7 mmol) as a solid to be be a flower of the title compound (1.5 g, 5.7 mmol) as a solid to be be a flower of the title compound (1.5 g, 5.7 mmol) as a solid to be be a flower of the title compound (1.5 g, 5.7 mmol) as a solid to be be a flower of the title compound (1.5 g, 5.7 mmol) as a solid to be be a flower of the title compound (1.5 g, 5.7 mmol) as a solid to be a flower of the title compound (1.5 g, 5.7 mmol) as a solid to be a flower of the title compound (1.5 g, 5.7 mmol) as a solid to be a flower of the title compound (1.5 g, 5.7 mmol) as a solid to be a flower of the title compound (1.5 g, 5.7 mmol) as a solid to be a flower of the title compound

6.16 an object to the EtOAd/CH₂Cl₂ is give the title defriction of the B. **B. 3'-Methody-Lyneholius-E-lyneholius-Assault**. **B. 3'-Methody-Lyneholius-E-lyneholius-Assault**.

- 30 3'-Methoxy-biphenyl-4-bromide (1.5 g, 5.7 mmol) is dissolved in 20 mL of THF and cooled to -78°C. To the solution is added a 2.5 M solution of the number of the solution in THF (2.3 mL, 5.7 mmol). The reaction mixture is stirred for 15 minutes and then is transferred via cannula to a solution of condensed sulfur dioxide gas (10 mL) in 40 mL of ether at 78°C. The solution is stirred for 30
 - minutes, allowed to warm to room temperature and then concentrated in vacuo.

 The resulting residue is triturated with ether to give 1 g of the lithium.

 biarylsulfinate as a solid. The solid is suspended in 15 mL of hexanes and

cooled to 0°C. To the suspension Is added a 1 M solution of sulfuryl chloride (4.2 mL, 4.2 mmol) in CH₂Cl₂. After 1 hour at 0°C, the resulting solution is concentrated. The residue is triturated with hexanes to give the title compound (0.6 g, 2.25 mmol) as a solid.

5 FAB MS, [M+H]*=267.

C. 3'-Methoxybiphenyl-4-sulfonic acid [1-3-(cyanobenzyl)-2-oxopyrrolidin-3-(S)-yllamide.

The title compound is prepared as described in EXAMPLE 1, Part D using 10 3'-methoxybiphenyl-4-sulfonyl chloride in place of 2-naphthalene sulfonyl chloride:

¹H NMR (CDCl₃, 300 MHz) δ 7.95 (d, 1H), 7.72 (m, 2H), 7.52 (m, 1H), 7.40 (m, 5H), 7.16 (d, 1H), 7.10 (d, 1H), 6.95 (d,1H), 5.33 (bs, 1H), 4.43 (AB, 2H), 3.88 (s, 3H), 3.81 (m, 1H), 3.24 (m, 2H), 2.64 (m, 1H) 2.07 (m, 1H).

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D. 3'-Methoxybiphenyl-4-sulfonic acid {1-[3-(aminoiminomethyl)benzyl]-2-oxopyrrolidin-3-(S)-yl}amide trifluoroacetate.

The title compound is prepared as described in EXAMPLE 1, Part E using 3'-methoxybiphenyl-4-sulfonic acid [1-3-(cyanobenzyl)-2-oxopyrrolidin-3-(S)-20 yl]amide as the starting material.

¹H NMR (DMSO-d₈, 300 MHz) δ 9.30 (bs, 2H), 9.05 (bs, 2H), 8.20 (d, 1H), 7.90 (m, 4H), 7.71 (m, 2H), 7.55 (m, 2H), 7.40 (m, 2H), 7.28 (m, 2H), 6.99 (d, 1H), 4.43 (AB, 2H), 4.18 (m, 1H), 3.82 (s, 3H), 3.12 (m, 1H), 2.05 (m, 1H), 1.62 (m, 1H). FAB MS, [M+H]⁺⁼⁴⁷⁹. Elemental analysis calculated with 1 mole of H₂O:

25 C=53.11%, H=4.79%, N=9.18%, found C=53.31%, H=4.51%, N=9.15%.

EXAMPLE 6

Naphthalene-1-sulfonic acid (1-[3-(aminoiminomethyl)benzyll-2-oxopyrrolidin -3-(S)-yllamide trifluoroacetate.

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A. Naphthalene-1-sulfonic acid [1-(3-cyanobenzyl)-2-oxopyrrolidin-3-(S)-yllamide.

The title compound is prepared as described in EXAMPLE 1, Part D using 1-naphthalene sulfonyl chloride in place of 2-naphthalene sulfonyl chloride.

¹H NMR (CDCl₃, 300 MHz) δ 8.67 (d, 1H), 8.28 (d, 1H), 8.06 (d, 1H), 7.96 (d, 1H), 7.67 (m, 2H), 7.55 (m, 2H), 7.38 (m, 2H), 7.19 (s, 1H), 5.52 (bs, 1H), 4.37 (AB, 2H), 3.75 (m, 1H), 3.14 (m, 2H), 2.40 (m, 1H), 1.97 (m, 1H).

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copied to 0°C. If the suspension is added a 1 Minorgon of suffici-B. Naphthalene-1-sulfonic acid (1-[3-(aminoiminomethyl)benzyl]-2oxopyrrolidin-3-(S)-yl)amide trifluoroacetate. and the sylneonous រៈ ១ជុះ១៤១ The title compound is prepared as described in EXAMPLE 1. Part E using naphthalene-1-sulfonic acid [1-(3-cyanobenzyl)-2-oxopyrrolidin-3-(S)-yl]amide as the starting material. ¹H NMR (DMSO-d_s, 300 MHz) δ 9.30 (b_s, 2H), 9.13 (b_s, 2H), 8.65 (d, 1H), 8.51 (d, 1H), 8.32 (d, 1H), 8.22 (d, 1H), 8.09 (d, 1H), 7.64 (m, 5H), 7.50 (m, 3H), 4.40 (AB, 2H), 4.17 (m, 1H), 3.07 (m, 1H), 1.89 (m, 1H), 1.53 (m, 1H). FAB MS, [M+H]+=423. Elemental analysis calculated with 1 mole of H2O: C=51.98%, H=4.54%, N=10.10%, found C=52.20%, H=4.17%, N=9.73% abnotice 'H MMR (CDCL 300 MHz) & 7.95 (d. 11%, 7.72 (m, 2H), 7.52 (m. 1H), 7.47 (m. 3H), 7.18 (d. 18) 7.10 (U. 18), 6.95 (d.18), 5.33 (bs. 18), 6.43 (Al. 5-Pyrid-2-ylthiophene-2-sulfonic acid (1-[3-(aminoiminomethyl)benzyl]-2oxopyrrolidin-3-(S)-yl}amide trifluoroacetate. A. 5-Pyrid-2-ylthiophene-2-sulfonic acid [1-(3-cyanobenzyl)-2-oxopyrrolidin-3the the company is separed as described in EXAMPE. The title compound is prepared as described in EXAMPLE 1, Part D using 5-pyrid-2-ylthiophene-2-sulfonyl chloride in place of 2-naphthalene sulfonyl Chloride. 148, 2d) 20 P. HS. 28. 03. 05. 2H. 9 C5 (bs. 2H. 9 C6. 2 1H NMR (CDCI₃, 300 MHz) δ, 8.62 (m, 1H), 7.78 (m, 1H), 7.69 (m, 1H), 7.58 (m, 2H), 7.50 (d, 1H), 7.46 (m, 2H), 7.20 (m, 2H), 5.43 (bs, 1H), 4.42 (AB, 2H), 3.98 (m, 1H), 3.26 (m, 2H), 2.68 (m, 1H), 2.15 (m, 1H). HEAT (HE C=53.11 & H=4 79%, N=3.18%, Itund C=83.3: 1 5-Pyrid-2-ylthiophene-2-sulfonic acid {1-[3-(aminoiminomethyl)benzyl]-2oxopyrrolidin-3-(S)-yl}amide trifluoroacetate. 8 3.14MAKS The title compound is prepared as described in EXAMPLE 1, Part E using 5-pyrid-2-ylthiophene-2-sulfonic acid [1-(3-cyanobenzyl)-2-oxopyrrolidin-3-(S)yl]amide as the starting material. ¹H NMR (DMSO-d_s, 300 MHz) δ 9,32 (bs, 2H), 9.13 (bs, 2H), 8,56 (d, 1H), 8.49 (d, 1H), 8.04 (d, 1H), 7.89 (m, 3H), 7.58 (m, 4H), 7.38 (m, 1H), 4.46 (AB, 2H), 4.23 (m, 1H), 3.16 (m, 2H), 2.16 (m, 1H), 1.70 (m, 1H). FAB MS, [M+H]*=456. Elemental analysis calculated: C=43.93%, H=3.39%, N=10.24%, found C=44.04%, H=3.43%, N=10.26%. C=44.04%, H=3.43%, N=10.26%. (a.if.,b) 30.5 (Hr.f.,b) 5 T., (a.f.,b) 6 (xHm) 30. (300) HMM Fr

> (44), "367 (m, 2H) 7.85 (c), 2H+ 7.38 (m), 2H), 7.13 (c), 1H). का है है के विकास में में विकास करा है। कि ले कि में में में में में में में में में

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Biphenyl-4-sulfonic acid (1-[3-(aminoiminomethyl)benzyl]-2-oxopyrrolidin-3-(S)-yl}amide trifluoroacetate.

Biphenyl-4-sulfonic acid [1-(3-cyanobenzyl)-2-oxopyrrolidin-3-(S)-yl]amide 5 The title compound is prepared as described in EXAMPLE 1, Part D using biphenyl-4-sulfonyl chloride in place of 2-naphthalene sulfonyl chloride. ¹H NMR (CDCl₃, 300 MHz) δ 8.14 (s, 1H), 7.95 (d, 1H), 7.82 (d, 1H), 7.64 (m, 5H), 7.47 (m; 6H), 5:42 (bs, 1H), 4.42 (AB, 2H), 3.82 (m, 1H), 3.22 (m, 1H), 2.62 65 (m; 1H); 2.13 (m; 1H); 6/60 (cm) (cm) (cm) (cm)

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B. Biphenyl-4-sulfonic acid (1-[3-(aminoiminomethyl)benzyl]-2-oxopyrrolidin-3-(S)-vllamide trifluoroacetate. Aid is the the common to the trifluoroacetate.

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The title compound is prepared as described in EXAMPLE 1, Part E using biphenyl-4-sulfonic acid [1-(3-cyanobenzyl)-2-oxopyrrolidin-3-(S)-yl]amide as

15: The starting materials to a good by 33 Fib., Mod CB (1000), Hide Ci ¹H NMR (DMSO-d₆, 300 MHz) δ (9.31 (bs, 2H), 9.14 (bs, 2H), 8.22 (d, 1H), 7.91 (m, 6H), 7.60 (m, 8H), 4.45 (AB, 2H), 4.16 (m, 1H), 3.12 (m, 1H), 2.07 (m, 1H), 1.65 (m, 1H)., FAB MS, [M+H]*=449. Elemental analysis calculated with 0.25 mole of H₂O: C=55.07%, H=4.53%, N=9.88%, found C=55.12%, H=4.41%, 20 N=10.05% radio of the Chebra of the targets of a superior decides

LES EXAMPLE 9000 entra a de la bitada tempo la Silitabatado e confere

ு 7-Methoxynaphthalene-2-sulfonic acid (1-[3-(aminoiminomethyl)benzyl]-2oxopyrrolidin-3-(S)-yl)amide trifluoroacetate. . (i), . . a. (m. 14. . (d. .)n. 3H), 7.30 (d. . (d.), 7.25 (m. 1H), 5.39 (d.)a. (1.25 (m. 1H), 5.39 (d.)a.

The transfer follows the many later to the following the majority of

(1) OAC17-Methoxynaphthalene-2-sulfonyl chloride. (18, 8) Se. 8 (18)

To a suspension of 7-hydroxynaphthalene-2-sulfonic acid, sodium salt (15 g, 60.9 mmol) in 150 ml of 2:1 H₂O/ethañol is added solld NaOH (2.68 g, 67 mmol) at room temperature. The mixture is stirred until a homogenous solution

30 dorms, and dimethyl sulfate (6.34 ml., 67 mmol) is then added. A precipitate eventually forms and the mixture is stirred over a period of 16 hours. The crude mixture is concentrated in vacuo and the residue is stirred in 100 mL of absolute EtOH as a slurry for 2 hours. The precipitate is filtered and dried. The solid is heated at reflux in 100 mL of 95% EtOH for 2 hours, allowed to cool to

room-temperature, filtered and dried to give 12.6 g of crude 7- no ent ு நிரும் இது இது மாகம் acid, sodium sait (12.6 g, 48.6 mmoi) in 20 mL of phosphorous oxychloride and ~ p

phosphorous pentachloride (13.2 g) 63.2 mmol) is heated slowly to 60°C until a homogenous solution forms and then is heated at 120°C for 4 hours. The resulting mixture is cooled in an ice bath and a mixture of ice/ice water is of maily readded slowly with stirring de mixture is diluted with water and extracted with 5 CHCl₃ (2x100 mL). The combined organic layers are washed successively with water, saturated NaHCO3 solution and saturated NaClly The organic phase is dried over anhydrous MgSQ, filtered and concentrated to give 10 g of a The crude product is purified by column chromatography in a gradient of 5% EtOAc/hexanes to 30% EtOAc/hexanes to afford the title compound (3.8 g, 14.8 mmol) as a white crystalline solid. 10 ¹H_NMR.(CDCl_s.,300,MHz),&8.49.(d,.1H),.7.96.(d,11H),-7.85.(d,12H),57.39 (dd, S-dibilorayg 1H), 7.29 (d, 1H), 3.99 (s, 3H). EI MS, [M] = 256 10, Hip ebims (iv-(2)) The 8-chloro-7-methoxynaphthalene-2-sulfonyl chloride (1:49 g, 5:12 mmol) is as some also isolated as a minor by-product from the above procedure; andici ¹H NMR (CDCl₃, 300 MHz) δ 8.95 (d, 1H), 8.01 (d₆1H), 7.90 (d₆2H); 7.55 (d, 19.5 (HE 151H), 4.09 (s. 3H) : EI MS; [M]+=290.3 (5HM 008 1,6-09MG) HMM H (m. EH), 7.60 (σ , 3H), 4.45 (AB, 2H), 4.15 (m, 1H), 3.12 (m, 1H), z 07 cm (Fig. as a max B. 7-Methoxynaphthalene-2-sulfonic acid [1-(3-cyanobenzyl)-2-oxopyrrolidinmole of H₂Or C=55.07%, H=4 58%. N=5.88%, found .abimafly-(2)-2 € € 19-6 20 The title compound is prepared from 3-(3-(S)-amino-2-oxopyrrolidin-1- 0S ylmethyl)benzonitrile hydrochloride as in EXAMPLE 1, Part D using 7methoxynaphthalene-2-sulfonyl chloride. The crude product; is triturated from 50% EtOAc/hexanes solution to give the title compound as a beige solid. 'H NMR (CDCl₃, 300 MHz) δ 8.38 (d, 1H), 7.91 (d, 1H), 7.81 (d, 1H), 7.73 (dd, 1H), 7.59 (m, 1H), 7.42 (m, 3H), 7.30 (dd, 1H), 7.25 (m, 1H), 5.39 (d, 1H), 4.45 25 (AB, 2H), 3.92 (s, 3H), 3.75 (m, 1H), 3.20 (m, 2H), 2.60 (m, 1H), 2.10 (m, 1H). To a suspension of 7-hydroxynaphthaleric is sulfonic acid, sodium gali (18.3). C. 7-Methoxynaphthalene-2-sulfonic acid (1-[3-(aminoiminomethyl)benzyl]-2dudulo: au oxopyrrolidin-3-(S)-yl)amide trifluoroacetate reservet muor te (lomm 30 7-Methoxynaphthalene-2-sulfonic acid [1-(3-cyanobenzyl)-2-oxopyrrolidin-3-(S)-yljamide is dissolved in 10 mL of a 2:1 mixture of EtOH/CH, Cl, and converted to the title compound as in EXAMPLE 1, Part E. The imidate intermediate is formed over a period of 18 hours at room temperature. The amidine formation occurred over a period of 18 hours at room temperature. The crude product is purified by RP-HPLC eluting in a gradient of 10% CH₃CN/H₂O (0.1% TFA) to 60% CH₃CN/H₂O (0.1% TFA) and the appropriate

product fractions are lyophilized to provide the title compound as a white solid.

¹H NMR (DMSO-d₆, 300 MHz) δ 9.41 (bs, 2H), 9.29 (bs, 2H), 8.33 (d, 1H), 8.19 (d, 1H), 7.96 (d, 1H), 7.87 (d, 1H), 7.68 (dd, 1H), 7.64 (m, 1H), 7.50 (m, 4H), 7.27 (dd, 1H), 4.36 (AB, 2H), 4.16 (dd, 1H), 3.48 (s, 3H), 3.04 (m, 2H), 1.93 (m, 1H), 1.59 (m, 1H). FAB MS, [M+H]*=453. Elemental analysis calculated with 1.7 mole of H_2O : C=50.28%, H=4.79%, N=9.38%; found C=50.27%, H=4.14%, N=9.07%.

7-Methoxynaphthalene-2-sulfonic acid {1-[3-(aminoiminomethyl)benzyl]-2-oxopyrrolidin-3-(R)-yl}amide trifluoroacetate is prepared from 7-methoxynaphthalene-2-sulfonic acid [1-(3-cyanobenzyl)-2-oxopyrrolidin-(3R)-yl]amide as above.

[文金][Ha] "新"(A) (H) (A) (15) (15) [3] [7]

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EXAMPLE 107

7-Ethoxynaphthalene-2-sulfonic acid (1-[3-(aminoiminomethyl)benzyl]-2oxopyrrolidin-3-(S)-ÿl}amide trifluoroacetate.

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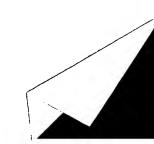
Can A.-7-Ethoxynaphthalene-2-sulfonyl chioride. 2016 A. M. C. S. S. S.

A 60% dispersion of sodium hydride (0.74 g, 18.45 mmol) in mineral oil is washed with hexanes twice and suspended in 35 mL of DMF. To this mixture is added slowly via an addition funnel 7-hydroxynaphthalene-2-sulfonic acid, 20 sodium salt (2.5 g, 10.1 mmol) in 50 mL of DMF at room temperature. The reaction mixture is stirred for 75 min during which time mild bubbling is observed (H2 evolution). The mixture is treated with promoethane (2.42 mL, 32.5 mmol) and stirred for 16 hours at room temperature. A little ice is added to decompose the excess NaH and the resultant mixture is concentrated in vacuo. 25 The residue is suspended in acetone and concentrated in vacuo two times and The solid is dried under high vacuum. The solid is suspended in acetone, filtered and dried to yield the crude 7-ethoxynaphthalene-2-sulfonic acid, sodium salt as a beige solid. A mixture of the sulfonic acid, sodium salt (3.77 g) in 10 mL of thionyl chloride is heated at 80°C for 2 hours. The mixture is allowed to cool to room temperature and concentrated in vacuo. The residue is diluted in EtOAc 30 and washed successively with water (2x), saturated NaHCO3 solution and saturated NaCl. The organic layer is dried over anhydrous MgSO₄, filtered and concentrated to yield 2:65 g of a crude brown oil. The crude product is purified by column chromatography in a gradient of 10% EtOAc/hexanes to 20% 35

35 EtOAc/hexanes to afford the title compound (1:67 g, 6:17 mmol) as a pale object. See a pale of the solid compound is a pale object. See a pale of the solid compound of the see are a see as a pale of the solid compound of the see are a see as a

H NMR (CDCI₃, 300 MHz) 8 8.46 (s, 1H), 7.97 (d, 1H), 7.85 (d) 1H), 7.84 (d, 1H), 7.38 (dd, 1H), 7.28 (s, 1H), 4.19 (q, 2H), 1:50 (t, 3H), 2.7 (Ht.b) . ART (dd, JH), 4 36 (AB, 2H), 4 16 (dd, 1H), 3 48 (c. 3H), 3.04 (m, 2H), 1.50 (m. 7-Ethoxynaphthalene-2-sulfonic acid [1-(3-cyanobenzyl)-2-oxopyrrolidin-3t.7 mole of H₂O: C=50.28%, H=4.79%, N=9.38°%; four-splinsfly-(2) The title compound is prepared from 3-(3-(S)-amino-2-oxopyrrolidin-1ylmethyl)benzonitrile hydrochloride as in EXAMBLE 1, Part D using 7ethoxynaphthalene-2-sulfonyl chloride. The crude product is triturated from 50% EtOAc/hexanes solution to give the title compound as a beige solid. ¹H NMR (CDCI₃ + DMSO-d₆, 300 MHz) δ 8.27 (d, 1H), 7.80 (d, 1H); 7.67 (m, 2H), 7.47 (m, 1H), 7.41 (bs, 1H), 7.34 (d, 2H), 7.17 (m, 3H), 4.34 (AB, 2H), 4.06 (q, 2H), 3.87 (m, 1H), 3.04 (m, 2H), 2.25 (m, 1H), 1.81 (m; 1H);;1:39(t, 3H). 7-Ethoxypachthatene-2-sulfonic acid (1-13-(aminoiminometry/benzyll-2) hoxvnaphthalene-2-sulfonic acid {1-[3-(aminoiminomethyl)benzyl]-2-15 oxopyrrolidin-3-(S)-vI}amide trifluoroacetate. 7-Ethoxynaphthalene-2-sulfonic acid [1=(3-cyanobenzyl)-2-oxopyrrolidin-3-(S)yllamide is dissolved in 10 mL of a 2:1 mixture of EtOH/CH2Cl2 and converted to the title compound as in EXAMPLE 1. Part E. The imidate intermediate is formed over a period of 18 hours at room temperature in The amidine formation occurred over a period of 48 hours at room temperature.) The crude product is purified by RP-HPLC eluting in a gradient of 10% CH3CN/H2O (0:1% TFA) to 60% CH₃CN/H₂O (0.1% TFA) and the appropriate product fractions are lyophilized to provide the title compound as a white solid, (loren 3.55 1H NMH (DMSO-d, 300 MHz) & 9.41 (bs, 2H), 9.33 (bs, 2H), 8.37 (d, 1H), 8.24 (d, 1H), 8.02 (d, 1H), 7.94 (d, 1H), 7.73 (dd, 1H), 7.70 (d, 1H), 7.56 (m; 4H), 7.32 (dd, 1H), 4.43 (AB, 2H), 4.17 (q, 2H), 4.15 (m, 1H), 3.10 (m, 2H), 2.00 (m, 1H), 1.59 (m, 1H), 1,40 (t, 3H). FAB MS, [M+H]*=467. Elemental analysis calculated with 1.9 mole of H₂O: C=50.91%, H=5.04%, N=9.13%; found C=50.92%, thionyl inforide is heated at 50°C for 2 hours room temperature and concentrated in year out and washed successively with water (2%, softwated Narius, sold of 5-Chloro-6-methoxynaphthalene-2-sulfonic acid [1-[3-] by be still se (aminoiminomethyl)benzyl]-2-oxopyrrolidin-3-(S)-yl}amide trifluoroacetate. by column informatography in a gradient of 10% EfCAc/hexands to 30 5-Chloro-6-methoxynaphthalene-2-sulfonyl chloride nexadioACE The title compound is prepared from 6-hydroxynaphthalene-2-sulfonic acid,

sodium salt as in EXAMPLE 9, Part A. The crude product mixture is purified by



column chromatography in a gradient of 5% EtOAc/hexanes to 10% EtOAc/hexanes to provide the title compound as a minor by-product. ¹H NMR (CDCl₃, 300 MHz) δ 8.57 (d, 1H), 8.42 (d, 1H), 8.05 (dd, 1H), 8.00 (d, 1H), 7.50 (d, 1H), 4.10 (s, 3H).

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B. 5-Chloro-6-methoxynaphthalene-2-sulfonic acid [1-(3-cyanobenzyl)-2oxopyrrolidin-3-(S)-yllamide.

The title compound is prepared from 3-(3-(S)-amino-2-oxopyrrolidin-1ylmethyl)benzonitrile hydrochloride as in EXAMPLE 1, Part D using 5-chloro-6methoxynaphthalene-2-sulfonyl chloride. The crude product is triturated from EtOAc to give the title compound as a beige solid. ¹H NMR (CDCl₃, 300 MHz) δ 8.44°(d, 1H), 8.38 (d, 1H), 7.98°(dd, 1H), 7.91 (d, 1H), 7.60 (m, 1H), 7.42 (m, 4H), 5.51 (d, 1H), 4.45 (AB, 2H), 4.09 (s, 3H), 3.80 (m, 1H), 3.20 (m, 2H), 2.60 (m, 1H), 2.10 (m, 1H). 15. The bt, 30 7 feet of 12 8 glit to 2 40 (that oct , 100 1) in

- C. 5-Chloro-6-methoxynaphthalene-2-sulfonic acid {1-[3-(aminoiminomethyl)benzyl]-2-oxopyrrolidin-3-(S)-yl)amide trifluoroacetate. 5-Chloro-6-methoxynaphthalene-2-sulfonic acid [1-(3-cyanobenzyl)-2oxopyrrolidin-3-(S)-yl]amide is dissolved in 10 mL of a 2:1 mixture of
- 20 EtOH/CH2Cl2 and converted to the title compound as in EXAMPLE 1, Part E. The imidate intermediate is formed over a period of 16 hours at room temperature. The amidine formation occurred over a period of 24 hours at broom temperature. The crude product is purified by RP-HPLC eluting in a gradient of 10% CH3CN/H5O (0.1% TFA) to 60% CH3CN/H5O (0.1% TFA) and
- 25 withe appropriate product fractions are lyophilized to provide the title compound coom temperature. The over a product is parified by fibliographia in a
- \(\text{A-1H NMR (DMSO-d}, 300 MHz)\δ 9.29 (bs, 2H), 9.10 (bs, 2H), 8.52 (d, 1H), 8.29 (d, 1H), 7.54 (bs, 1H), 7.52 (d, 1H), 4.41 (AB, 2H), 4.16 (m, 1H), 4.04 (s, 3H),
- 30 3.09 (m, 2H), 2.01 (m, 1H), 1.59 (m, 1H). FAB MS, [M+H]*=487. Elemental analysis calculated with 1.5 mole of H₂O: C=47.88%, H=4.32%, N=8.93%: ☐ Gound C=47.88%, H=3.88%, N=8.48%. 3 (34 L.m) \$1 \$ (HS E) 11 j. 1.60 (in 11th, 182 m). jM+H*=617. Edeman, J. angly, in calculated the

Perof H.O. CHAR BRIN, HARDON, NO. 1420 CORD 12 1000 CHARGES 24 CO.

5-Chloro-6.7-dimethoxynaphthalene-2-sulfonic acid {1-[3-35 (aminoiminomethyl)benzyl]-2-oxopyrrolidin-3-(S)-yl}amide trifluoroacetate. 81 (田)和(2)(3)

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A. 5-Chloro-6.7-dimethoxynaphthalene-2-sulfonyl chloride. amulou The title compound is prepared from 6,7-dihydroxynaphthalene-2-sulfonic acid, sodium salt hemihydrate as in EXAMPLE 9, Part A. The crude product mixture is purified by column chromatography in a gradient of 5% EtOAc/hexanes to 30% EtOAc/hexanes to give the title compound as a minor by-product. ¹H.NMR (CDCl₃, 300 MHz) δ 8.48 (d, 1H), 8.38 (d, 1H), 7.45 (dd, 1H), 7.30 (s, 1H), 4.05 (s, 3H), 4.00 (s, 3H). apirocijyde o nicilanwa co The title composite traverse from 1-(3-43)-aminu-2-overcynolo-B. 5-Chloro-6.7-dimethoxynaphthalene-2-sulfonic acid [1-(3-cvanobenzyl)-2oxopyrrolidin-3-(S)-yllamide shorts for the seemeless aparty or the control of the seemeless and the seemeless of the seemele The title compound is prepared from 3-(3-(S)-amino-2-oxopyrrolidin-1ylmethyl)benzonitrile hydrochloride as in EXAMPLE,1; Part D'using 5-chloro-6,7-dimethoxynaphthalene-2-sulfonyl chloride. The crude product is triturated from EtOAc to give the title compound as a beige solid. 32 8 (Ht.,m) $^{1}\text{H NMR (CDCI}_{3}$, 300 MHz) δ 8.49 (d, 1H), 8.25 (d, 1H), 7.86 (dd, 1H), 7.55 (m, 1H), 7.40 (m, 3H), 7.20 (s, 1H), 5.89 (m, 1H), 4.44 (AB; 2H), 4.03 (s, 3H), 4.00 (s, 3H), 3.86 (m, 1H), 3.20 (m, 2H), 2.59 (m, 1H), 2.07 (m, 1H), 20 (ms 5 Chloro-Car etho graphthale no-2-sulford soid (1-(3-chenobet tylug-.C. 5-Chloro-6.7-dimethoxynaphthalene-2-sulfonic acid (1-[3-young 20 (aminoiminomethyi)benzyl]-2-oxopyrrolidin-3-(S)-yl)amide trifluoroacetate. 5-Chloro-6,7-dimethoxynaphthalene-2-sulfonic acid [1-(3-cyanobenzyl)-2oxopyrrolidin-3-(S)-yl]amide is dissolved in 10 mL of a 2:1 mixture of EtOH/CH2Cl2 and converted to the title compound as in EXAMPLE 1, Part E. The imidate intermediate is formed over a period of 24 hours at room temperature. The amidine formation occurred over a period of 24 hours at room temperature. The crude product is purified by RP-HPLC eluting in a gradient of 10% CH₃CN/H₂O (0.1% TFA) to 60% CH₃CN/H₂O (0.1% TFA) and the appropriate product fractions are lyophilized to provide the title compound as a white solid. A first JA rab (diff.b) Sec. (HF red) + 7 (HF re) ¹H NMR (DMSO-d₆, 300 MHz) δ 9.29 (bs. 2H), 9.12 (bs. 2H), 8.43 (d, 1H), 8.30 (d, 1H), 8.19 (d, 1H), 7.87 (dd, 1H), 7.73 (s, 1H), 7.67 (m, 1H), 7.55 (m, 3H), 4.41 (AB, 2H), 4.14 (m, 1H), 3.97 (s, 3H), 3.89 (s, 3H), 3.08 (m; 2H), 1.99 (m, 1H), 1.60 (m, 1H). ISP MS, [M+H]+=517. Elemental analysis calculated with 1.5 mole of H₂O: C=47.38%, H=3.91%, N=8.14%; found C=47.40%, H=4.05%,

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Dibenzofuran-2-sulfonic acid {1-[3-(aminoiminomethyl)benzyl]-2-oxopyrrolidin-3-(S)-yl)amide trifluoroacetate.

A. Dibenzofuran-2-sulfonic acid [1-(3-cyanobenzyl)-2-oxopyrrolidin-3-(S)-Company on the con-

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5 yllamide, second

> The title compound is prepared from 3-(3-(S)-amino-2-oxopyrrolldin-1ylmethyl)benzonitrile hydrochloride as in EXAMPLE 1, Part D using 2dibenzofuransulfonyl chloride. The crude product is triturated from EtOAc to give the title compound as a beige solid.

- 10 ¹H NMR (CDCl₃, 300 MHz) δ 8.59 (d, 1H), 8.04 (dd, 1H), 7.95 (d, 1H), 7.64 (d, 1H), 7.60 (m, 1H), 7.52 (m, 2H), 7.40 (m, 5H), 4.42 (AB, 2H), 3.89 (m, 1H), 3.19 (m, 2H), 2.57 (m, 1H), 2.08 (m, 1H), 4 14 7 2 (5 114) 2 (2) (3) (4) 2) 5 T 111 g) 85 85 1
 - B. Dibenzofuran-2-sulfonic acid (1-13-(aminoiminomethyl)benzyll-2oxopyrrolidin-3-(S)-yl}amide trifluoroacetate.
- 15 Dibenzofuran-2-sulfonic acid [1-(3-cyanobenzyl)-2-oxopyrrolidin-3-(S)yl]amide is dissolved in 10 mL of a 2:1 mixture of EtOH/CH2Cl2 and converted to the title compound as in EXAMPLE 1, Part E. The imidate intermediate is formed over a period of 24 hours at room temperature. The amidine formation
- 20 occurred over a period of 40 hours at room temperature. The crude product is purified by RP-HPLC eluting in a gradient of 10% CH₃CN/H₂O (0.1% TFA) to 60% CH₃CN/H₂O (0.1% TFA) and the appropriate product fractions are lyophilized to provide the title compound as a white solid.
- 25 (d, 1H), 8.22 (d, 1H), 8.04 (dd, 1H), 7.92 (d, 1H), 7.79 (d, 1H), 7.67 (m, 1H), 7.61 (m, 2H), 7.56 (m, 1H), 7.55 (bs, 1H), 7.48 (m, 1H), 4.42 (AB, 2H), 4.19 (m, 1H), 3.10 (m, 2H), 2.04 (m, 1H), 1.61 (m, 1H). FAB MS, [M+H]*=463. Elemental analysis calculated with 1.3 mole of H,O: C=51.97%, H=4.31%, N=9.32%: found C=51.99%, H=3.76%, N=9.00%; 1 states to 22-E-35-86 and 22-E-

R-CV: Frankhonapothaliana 2 sukonio acid [1-(1-uyunohenzy))-z-

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EXAMPLEM 4 TO THE COLOR OF THE

7-Aminonaphthalene-2-sulfonic acid (1-[3-(aminoiminomethyl)benzyl]-2oxopyrrolidin-3-(S)-yl)amide bistrifluoroacetate. the amidine formation occurred over a pency of 16 hours, it

35 A. N-Cbz-7-aminonaphthalene-2-sulfonyl chloride. To a suspension of 7-aminonaphthalene-2-sulfonic acid, sodium salt (3 g, 12.2 mmol) in 70 mL of water is added solid NaOH (0.98 g, 24 mmol) at room

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temperature. The mixture is stirred for 30 minutes, and benzyl chloroformate (3.43 mL, 24 mmol) is then added. The resulting mixture is stirred over a period of 16 hours. The crude product is treated as in EXAMPLE 9, Part A, to give 4.18 g of crude N-CBz-7-aminonaphthalene-2-sulfonic acid, sodium salt.

A mixture of the sulfonic acid, sodium salt (4.18 g, 11 mmol) in 12 mL of thionyl chloride is heated at 80°C for 3 hours. The mixture is allowed to cool to room temperature and concentrated in vacuo. The residue is diluted with EtOAc and washed successively with water (2x); saturated NaHCO₃ solution and saturated NaCl. The organic layer is dried over anhydrous MgSO₄; filtered and concentrated to give a brown-oil. The crude product is purified by column chromatography in a gradient of 10% EtOAc/hexanes to 30% EtOAc/hexanes to afford the title compound (1.76 g, 4.68 mmol) as a beige solid. (11)

H NMR (CDCl₃, 300 MHz) & 8.38 (s, 1H), 8.12 (s, 1H), 7.88 (d, 1H), 7.80 (d, 2H), 7.60 (dd, 1H), 7.34 (m, 5H), 7.27 (s, 1H), 5.21 (s, 2H)

B. N-Cbz-7-aminonaphthalene-2-sulfonic acid [1-(3-cyanobenzyl)-2-oxopyrrolidin-3-(S)-yllamide. The strength of the bevious half she intervious hal

The title compound is prepared from 3-(3-(S), amino-2-oxopyrrolidin-1-ylmethyl) benzonitrile hydrochloride as in EXAMPLE 1; Part D using N-Cbz-7-aminonaphthalene-2-sulfonyl chloride. The crude product is purified by column chromatography using a gradient of 10% EtOAc/CH₂Cl₂ to 25% EtOAc/CH₂Cl₂ to give the title compound as a solid.

1H NMR (CDCl₃, 300 MHz) 8 831 (s, 1H), 8.03 (s, 1H), 7.71 (m, 3H); 7.55 (m, 2H) 7.40 (m, 2H) 5.78 (c, 1H) 5.25 (d, 1H) 5.91 (d, 1H) 4.44 (AB-OH) 2.95

2H), 7, 40 (m, 9H), 5.78 (s, 1H), 5.25 (d, 1H), 5,21 (d, 1H), 4,41 (AB; 2H), 3.85 (m, 1H), 3.15 (m, 2H), 2.53 (m, 1H), 2.02 (m, 1H).

Oxopyrrolidin-3-(S)-yl)amide bistrifluoroacetate.

N-Cbz-7-aminonaphthalene-2-sulfonic acid [1-(3-cyanobenzyl)-2-oxopyrrolidin-3-(S)-yl]amide is dissolved in 10 mL of a 2:1 mixture of EtOH/CH₂Cl₂ and converted to the title compound as in EXAMPLE 1, Part E. The imidate intermediate is formed over a period of 18 hours at room temperature. The amidine formation occurred over a period of 18 hours at room temperature. The crude product is purified by RP-HPLC eluting in a gradient of 10% CH₃CN/H₂O (0.1% TFA) to 60% CH₃CN/H₂O (0.1% TFA) and

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the appropriate product fractions are lyophilized to provide the title compound as a white solid.

¹H NMR (DMSO-d₆, 300 MHz) δ 9.29 (bs, 2H), 9.20 (bs, 2H), 8.11 (d, 1H), 8.08 (s, 1H), 7.82 (d, 1H), 7.72 (d, 1H), 7.67 (m, 1H), 7.55 (m, 3H), 7.48 (dd, 1H), 7.13 (dd, 1H), 7.00 (d, 1H), 5.11 (bs, 3H), 4.42 (AB, 2H), 4.12 (m, 1H), 3.06 (m, 2H), 1.94 (m, 1H), 1.56 (m, 1H). FAB MS, [M+H]*=438. Elemental analysis calculated with 0.8 mole of H₂O: C=45.96%, H=3.94%, N=10.31%; found C=45.97%, H=4.02%, N=10.41%:

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10% /EXAMPLE(15) | Sept. 6.00.0000 | 10.006 (6.00.60.000)

Naphthalene-2-sulfonic acid (1-[4-(aminoiminomethyl)benzyl]-2-oxopyrrolidin-3-(S)-yl)amide trifluoroacetate. Common trifl

A. [1-(4-Cyanobenzyl)-2-oxopyrrolidin-3-(S)-yl]carbamic acid tert-butyl ester.

The title compound is prepared from Boc-L-Asp(H)-OBn as in EXAMPLE 1, Part B, using p-cyanobenzylamine hydrochloride in place of m-cyanobenzylamine hydrochloride. The crude residue is purified by column chromatography eluting with a gradient of 20% EtOAc/CH₂Cl₂ to 40% EtOAc/CH₂Cl₂ to give the title compound as a white solid.

¹H NMR (CDCl₃, 300 MHz) δ 7.62 (d, 2H), 7.31 (d, 2H), 5.15 (bs, 1H), 4.53 (AB, 2H), 4.21 (m, 1H), 3.24 (m, 2H), 2.61 (m, 1H), 1.90 (m, 1H); 1.46 (s, 9H).

B.164-(3-(S)-Amino-2-oxopyrrolidin-1-ylmethyl)benzonitrile hydrochloride.
பார் ் The title compound is prepared as a white solid from [1-(4-cyanobenzyl)-2-ெ 25-- oxopyrrolidin-3-(S)-yl]carbamic acid tert-butyl esterias described in EXAMPLE

тим канайн NMR-(DMSO-d₆, 300 MHz) 8 8 65 (bs, 3H), 7 8 (d, 2H), 7 .49 (d, 2H), 4.54 (d, 2H), 4.54 (d, 2H), 4.68 (m, 1H), 3 .30 (m, 2H), 2 .40 (m, 1H), 2 .01 (m, 1H). 8 .40 (m, 1H), 2 .01 (m, 1H).

or 90/30 C. Naphthálene-2-súlfónic acid [1-(4-cyanobenzyl)-2-oxopyrrolidin-3-(S)-yl]amide.

The title compound is prepared from 4-(3-(S)-amino-2-oxopyrrolidin-1'ylmethyl)benzonitrile hydrochloride as in EXAMPLE 1, Part D. The crude
product is triturated from EtOAc to give the title compound as a white solid. 'H
NMR (DMSO-d_s, 300 MHz) 8 8.50 (s, 1H), 8.00 (m, 2H), 7.93 (m, 3H), 7.65 (m,
5H), 7.28 (m, 1H), 4.45 (AB, 2H), 3.80 (m, 1H), 3.20 (m, 2H), 2.55 (m, 1H), 2.11
(m, 1H).

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Naphthalene-2-sulfonic acid; [1-(4-cyanobenzyl)-2-oxopyrrolidin-3-(S)-yl]amide is dissolved in 10 mL of a 2:1 mixture of EtOH/CH₂Cl₂ and converted to the title compound as in EXAMPLE 1; Part E. The imidate intermediate is formed over a period of 18 hours at room temperature. The amidine formation occurred over a period of 48 hours at room temperature: The crude product is purified by RP-HPLC eluting in a gradient of 10% CH₃CN/H₂O (0.1% TFA) to 60%

10 CH₃CN/H₂O (0.1% TFA) and the appropriate product fractions are lyophilized to provide the title compound as a white solid pinciles - S-ansisturios vi

¹H NMR (DMSO-d₆, 300 MHz) δ 9.26 (bs, 2H), 9.10 (bs, 2H), 8.49 (d, 1H), 8.30 (d, 1H), 8.12 (d, 1H), 8.11 (d, 1H), 8.03 (d, 1H), 7.88 (dd, 1H), 7.74 (d, 2H), 7.68 (m, 2H), 7.40 (d, 2H), 4.44 (AB, 2H), 4.17 (m, 1H), 3.07 (m, 2H), 2.01 (m, 1H),

15 a. 1.58 (m, 1H); (FAB MS, [M+H]*=423; Elemental analysis calculated with 1.4 mole of H₂O; C=51.32%, H=4.63%, N=9.97%; found C=51.32%, H=4.36%, V=9.97%; found C=51.32%, H=4.36%, V=9.78%; number of being a cubic and captured analysis calculated with 1.4

whiling with a gradient of 20% EtOAciCH, Chylologist Etonough, Cl. Light title compound area value actid

3A 2.20 - 7-Methoxynaphthalene-2-sulfonic:acid [1-(3-aminomethylbenzyl)-2- σορογιτοlidin-3-(S)-yl]amide trifluoroacetate σες (Hε σε εξε (Hε

To a solution of 7-methoxynaphthalene-2-sulfonic acid [1-(3-cyanobenzyl)-2-oxopyrrolidin-3-(S)-yl]amide (0.12 g, 0.27 mmol) in 10 mL of 7 N NH₃/MeOH is added a catalytic amount of 5% rhodium on alumina powder the resulting mixture is hydrogenated at room temperature on a Paar apparatus at 50 p.s.i. for 3 hours. The crude mixture is filtered through a pad of Celite; washed with MeOH (2x10 mL) and concentrated in vacuo. (The crude product is purified by RP-HPLC eluting in a gradient of 10% CH₃CN/H₂O (0.1% TFA) to 60%

30 CH₂CN/H₂O (0.1% TFA) and the appropriate product fractions are lyophilized to provide the title compound as a white solid.

1H NMR (DMSO-d_e, 300 MHz) δ 8.39 (d, 1H), 8.21 (d, 1H), 8.13 (bs. 3H), 8.01 (d, 1H), 7.93 (d, 1H), 7.71 (dd, 1H), 7.55 (d, 1H), 7.32 (m, 3H), 7.20 (m, 2H), 4.30 (AB, 2H), 4.10 (m, 1H), 4.00 (m, 2H), 3.90 (s, 3H), 3.03 (m, 2H), 1.96 (m, 3H), 1.55 (m, 1H). FAB MS, [M+H]:=440 (shift) Composite the same statement of the same state

 Naphthalene-2-sulfonic acid (1-[3-(aminoiminomethyl)benzyll-2-oxopyrrolidin-3-(S)-vI}methvl amide trifluoroacetate.

A. Naphthalene-2-sulfonic acid [1-(3-cyanobenzyl)-2-oxopyrrolidin-3-(S)-

vllmethyl amide. 5

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Naphthalene-2-sulfonic acid [1-(3-cyanobenzyl)-2-oxopyrrolidin-3-(S)-yl]amide (0.3 g, 0.74 mmol) is dissolved in 9 mL of an 8:1 mixture of THF/DMF and cooled to 0°C. Sodium hydride (30 mg of a 60% dispersion in mineral oil, 0.75 mmol) is added and the solution is stirred for 15 minutes. To the mixture is

10 : A added methyl lodide (0.33 g, 2.34 mmol). The cooling bath is removed and the solution is stirred at room temperature for 2 hours. The solution is poured into a separatory funnel and diluted with 100 mL of EtOAc. The organic layer is washed with 1: N/HCI, dried over MgSO, and concentrated. The residue is purified by column chromatography eluting with 10% EtOAc/CH, Clato give the

15 filtle compound (0.23 g, 0.52 mmol) as a solid! (0.10 100) Auf 14 NMR (CDCI₃, 300 MHz) δ 8.52 (s, 1H), 8.00 (m, 4H), 7.62 (m, 4H), 7.48 (m, 3H), 4.95 (m, 1H), 4.45 (AB, 2H), 3.20 (m, 1H), 2.80 (s, 3H), 2.37 (m, 1H), 2.05 (m, 1H). FAB MS, [M+H]+=420.

20. 3 B. Naphthalene-2-sulfonic acid {1-[3-(aminoiminomethyl)benzýlj-2and accompanied in a companied with a companied in the co

214), 7.50 (m. 3H), 7.31 (m. 1m, 5.04 (d. 1H), 3.92 (m. 1H), 3.05 (d. 2H), 206

COMPANY CONTROLLING COMPOUND IS prepared as described in EXAMPLE 1. Part E using;naphthalene-2-sulfonic acid [1-(3-cyanobenzyl)-2-oxopyrrolidin-3-(S)stired for a hours. The tea Allahamaterial is not permit being material is not permit and a not being a stire starting material.

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25 H-NMRs(DMSO-d_{st} 300 MHz) δ 9.30 (bs, 2H) 9.10 (bs, 2H); 8.52 (s, 1H), 8.15 ટ કાઇન(m, 3H), 7:85 (d,ધH), 7:68 (m, 3H), 7:55 (m, 3H), 4:98 (m, 1H), 4:42 (AB, 2H). □ 1 5 (m, 2H), 2:69 (s, 3H), 2:02 (m, 1H), 1:82 (m, 1H). FAB MS, [M+H]+=437. Elemental analysis calculated with 2 mole of H₂O: C=51.19%, H=4.985%, (40) #6 \ N=9.55%, found C=51.01%, H=4.35%, N=9.10%.000 (100.0) AMN

EXAMPLE 18

Naphthalene-2-sulfonic acid (1-[3-(aminoiminomethyl)benzyl]-pyrrolidin-3-(S)-O. Naphthalene-8-sulfonic acid [1-[3-cm]stepacoroulfintaldacime[iv_miles... the ellectude bistrilluoruscetatu.

(m. 185) 2.45 (m, 28t) 2.18 (a), ...45, 1.79 (m. 194

-S 35 AGNaphthalene-2-sulfonic acid-N-Boc-3-(S)-aminobyrrolidine de adi N-Boc-3-aminopyrrolidine (1.09 g) 5.83 mmol) is dissolved in 30 mL of CH₂Cl₂. To the solution is added triethylamine (0.61 g, 6.02 mmol) followed by 2naphthalene sulfonyl chloride (1.32 g) 5.83 mmol). The reaction mixture is stirred for 4 hours. The crude mixture is diluted with 150 mL of EtOAc and washed with 1 N HCl, 10% Na₂CO₃ and saturated NaCl. The organic layer is 3). E. dried over MgSO4, filtered and concentrated to give the title compound (2.19 g. yilmethyi socide.

5.8 mmol) as an oil.

ir.

spice 1. - 21H NMR (CDC), 300 MHz) οιδείδει (s. 1H); 7.95 (m; 4H), 7.66 (m; 3H), 5.03 րութ (bsr.վ.H), 3.88 (m;վ.H)ը3.30 (m, 2H), 3.10 (m,:1H), վ.95 (m, 2H)ը1(45) (s, 9H).

രാവധി ര സി. Sodium hydride (60 mg of a 60% dispersion in mineral cri. 073

B. Naphthalene-2-sulfonic acid-pyrrolidin-3-(S)-ylamide trifluoroacetate.

Naphthalene-2-sulfonic acid-N-Boc-3-(S)-aminopyrrolidine (1.8 g) 4:78 mmol) is dissolved in 50 mL of CH2Cl211 Trifluoroacetic acid (8 mL) is added dropwise. The reaction mixture is stirred for 16 hours. The solution is concentrated in

vacuo and then reconcentrated from toluene to give the title compound (1.8 g.

purified by column chromatography eluting with 10% Etc (lomm 46.4), give the

¹H NMR (CDCl₃, 300 MHz) ₂ δ (9.10 (bs, 1H), 8.82 (bs, 1H), 8.39 (s, 1H), 7.90 (m, 3H), 7.78 (d, 1H), 7.61 (m, 3H); 4.00 (bs; 1H), 3.5 (m, 2H); 3.38 (m, 2H).

2H), 4.95 (m, 1H) 4 45.(AB 2H), 9.20 (m, 1H) 2.80 (c.3(H2.3m) 20.5 (H) 2.00

(m), 1H). FAB MS PALHP=420. C. Naphthalene-2-sulfonic acid [1-(3-cvanobenzyl)-pyrrolidin-3-(S)-yl]amide.

- Naphthalene-2-sulfonic acid-pyrrolidin-3-(S)-ylamide trifluoroacetate (0.52 g, 20 1.34 mmol) is dissolved in 7 mL; of DMF. (Triethylamine (0.16 q. 1.6 mmol) is added and the reaction mixture is cooled to 0°C αα-Bromo-m-toluyl nitrile (0.25 .(2) gill.27 mmol) is added and the mixture is warmed to room temperature and stirred for 2 hours. The reaction mixture is diluted with 150 mL of EtOAc and
- the solution is washed with 1 N HCl, 10% Na₂CO₃ and saturated NaCl. The Expression and concentrated. The residue is + Fife (purified by column chromatography, eluting with 50% EtOAc/CH2Cl3 to give the title compound (0.2 g, 0.51 mmol) as an oil should also be the more id-¹H NMR (CDCl₃, 300 MHz) δ 8.40 (s, 1H), 7.95 (m, 3H), 7.80 (d, 1H), 7.64 (m,
 - 2H), 7.50 (m, 3H), 7.31 (m, 1H), 5.04 (d, 1H), 3.92 (m, 1H), 3.05 (q, 2H), 2:70 30 (m, 1H), 2.40 (m, 2H), 2.18 (m, 2H), 1.59 (m, 1H).

PlayInhalene-2-sulfonic and ci-fa-faminoiminometholiber syll-nymin is nearly D. Naphthalene-2-sulfonic acid (1-[3-(aminoiminomethyl)benzyl]-pyrrolidin-3-(S)-vI)amide bistrifluoroacetate.

The title compound is prepared as in EXAMPLE, 1. Part E using naphthalene-2-35 sulfonic acid [1-(3-cyanobenzyl)-pyrrolidin-3-(S)-yl]amide as the starting an material with manifer and the color of the second of th

¹H NMR (CDCl₃, 300 MHz) δ 10.6 (bs, 1H), 9.32 (bs, 3H), 8.45 (s, 1H), 8.14 (m, 2H), 8.05 (d, 1H), 7.72 (m, 9H), 3.85 (m, 1H), 3.65 (AB, 2H), 3.25 (m, 4H), 1.95 (m, 2H). FAB MS, [M+H]⁺=409. Elemental analysis calculated with 1.25 mole of H_2O : C=47.39%, H=4.36%, N=8.50%, found C=47.12%, H=3.97%, N=8.50%.

EXAMPLE 19

7-Methoxynaphthalene-2-sulfonic acid (1-[3-(aminoiminomethyl)benzyl]-2.5-dioxopyrrolidin-3-(S)-yl}amide trifluoroacetate.

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A. N-Boc-Asp-(m-cyanobenzylamine)-OBn.

Boc-Asp-OBn (3.23 g, 10 mmol) is dissolved in 100 mL of THF. Triethylamine (2.53 g, 25 mmol) is added followed by m-cyanobenzylamine hydrochloride (1.75 g, 10.4 mmol). The reaction mixture is cooled to -10°C, and the BOP

- reagent (4.42 g, 10 mmol) is added. The mixture is stirred for 16 hours. The crude mixture is diluted with 200 mL of EtOAc and washed with 1 N HCl, 10% Na₂CO₃ and saturated NaCl. The organic layer is dried over MgSO₄, filtered and concentrated. The residue is purified by column chromatography eluting with 20% EtOAc/CH₂Cl₂ to give the title compound
- 20 (3.4 g, 7.8 mmol) as a solid.

 'H NMR (CDCl₃, 300 MHz) δ 7.48 (m, 9H), 7.00 (bs, 1H), 5.68 (bs, 1H), 5.15 (AB, 2H), 4.60 (m, 2H), 4.35 (dd, 1H), 3.12 (dd, 1H), 2.75 (dd, 1H), 1.45 (s, 9H).

B. (1-(3-Cyanobenzyl)-2.5-dioxopyrrolidin-3-(S)-yllcarbamic acid tert-butyl ester.

N-Boc-Asp-(m-cyanobenzylamine)-OBn (1 g, 2.08 mmol) is dissolved in 20 mL of THF and cooled to -78°C. A 1 M solution of lithium hexamethyldisilylazide (4.8 mL, 4.8 mmol) in THF is added dropwise. The mixture is stirred for 20 minutes and 20 mL of saturated NH₄Cl is added. The solution is extracted with

- 30 EtOAc and then washed with 1 N HCl, 10% Na₂CO₃ and saturated NaCl. The organic layer is dried over MgSO₄, filtered and concentrated. The residue is purified by column chromatography eluting with 20% EtOAc/CH₂Cl₂ to give the title compound (0.65 g, 1.8 mmol) as a solid.
 - (bs, 1H), 4.75 (AB, 2H), 4.20 (m, 1H), 3.10 (dd, 1H), 2.89 (dd, 1H), 1.45 (s, 9H).
 - C. 3-(3-(S)-amino-2.5-dioxopyrrolidin-1-ylmethyl)benzonitrile hydrochloride.

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<u>19139</u>

The title compound is prepared as in EXAMPLE 1, Part Cousing 1-(3cyanobenzyl)-2,5-dioxopyrrolidin-3-(S)-yl]carbamic acid tert-butyl ester as the starting material. starting material.

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Starti 4.45 (m, 1H), 3.12 (dd, 1H), 2.80 (dd, 1H). N=8.50%

> D. 7-Methoxynaphthalene-2-sulfonic acid [1-(3-cyanobenzyl)-2.5dioxopyrrolidin-3-(S)-yl]amide.

₽.

Z-Methoxyuachthalene-2-sulfonic The title compound is prepared as in EXAMPLE 1, Part D using 3-(3-(S)-

amino-2,5-dioxopyrrollidin-1-ylmethyl)benzonitrile hydrochloride and 10 7-methoxynaphthalene-2-sulfonyl chloride.

1H NMR (CDCl₃, 300 MHz) 8 8.31 (s, 1H), 7.91 (d, 1H), 7.81 (d, 1H), 7.70 (d, 1H) in the DCL of baylogab of the many control of the baylogab of the many control of the baylogab o

1H), 7.56 (m, 2H), 7.35 (m, 2H), 7.21 (m, 2H), 5.39 (bs. 1H), 4.62 (AB, 2H), 4.12 (m, 1H), 3.92 (s, 3H), 3.15 (dd, 1H), 2.90 (dd, 1H), 3.92 (s, 3H), 3.15 (dd, 1H), 2.90 (dd, 1H), 3.92 (s, 3H), 3.15 (dd, 1H), 2.90 (dd, 1H), 3.92 (s, 3H), 3.15 (dd, 1H), 3.92 (dd, 1H), 3.92 (s, 3H), 3.15 (dd, 1H), 3.90 (dd, 1H), 3.92 (s, 3H), 3.15 (dd, 1H), 3.90 (dd, 1H), 3.92 (s, 3H), 3.15 (dd, 1H), 3.90 (dd, 1H

E. 7-Methoxynaphthalene-2-sulfonic acid (1-[3-(aminoiminomethyl)benzyl]reagent (4.42 g, 10 minol) is added. The mixture

2.5-dioxopyrrolidin-3-(S)-yl\amide trifluoroacetate. N 201 10H N 1 The title compound is prepared as in EXAMPLE 1, Part E using 75%

ການຕົ້ງໃດ ເປັນຄົ້ງກາວ ສີເປັນກິເຊັນ ອີຊີໄດ້ ເປັນກາກອອກບວ ຄາເສ ກອງອີດ. ການກິເຊັນ ການກິເຊັນ ການກິເຊັນ ອີຊີໄດ້ ເປັນ methoxynaphthalene-2-sulfonic-acid (1-(3-cyanobenzyl)-2,5-dioxopyrrolidin-3-20 (S)-yl]amide as the starting material.

¹H NMR (DMSO-d₆, 300 MHz) δ 9.29 (bs, 2H), 9.18 (bs, 2H), 8.42 (d, 1H), 8.39 (s 1H), 9.6 (d 1H), 2.00 (d 1H), 2.00 (d 1H), 3.00 (d 8.39 (s, 1H), 8.05 (d, 1H), 7.95 (d, 1H), 7.70 (m, 3H), 7.48 (m, 3H), 7.37 (d, 1H), 4.68 (m, 3H), 3.89 (s, 3H), 2.80 (dd, 1H), 2.32 (dd, 1H) FAB MS, [M+H]+=467.

Elemental analysis calculated with 1.75 mole of H₂O: C=49.06%, H=4.36%, 25 N=9.15%, found C=48.99%, H=4.17%, N=8.98%.

N-Bee-Asp-(m. eyanobenzylamine)-O6n (1.9. 2.08 mm). History at 20 mt.

3-yilamide trifluoroacetate.

minutes and 20 muloi saturated NR₂Otts added

A bear where both OO. at 1,201 (1.1) A 1 gray bedrew nedt both AO. 3-[(N-Boc)-3-amino-2-oxopiperidin-1-ylmethyl]-benzonitrile. A mixture of N-2-Boc-L-ornithine (1.5 g, 6.45 mmol) and 3-cyanobenzaldehyde (0.42 g, 3.23 mmol) are suspended in 20 mL of MeOH. A solution of anhydrous zinc chloride (0.24 g, 1.79 mmol) and sodium cyanoborohydride (0.22 g, 3.5 mmol) in 5 mL of MeOH is added. The mixture is stirred for 16 hours at room temperature. After this time, 20 mL of 1 N NaOH is added. The solution is

concentrated and the residue is partitioned between EtOAc and water. The

20

- organic layer is washed with saturated NaCl. The organic layer is dried over MgSO₄, filtered and concentrated to give N-α-Boc-N-δ-(3-cyanobenzyl)-L-ornithine. A portion of the crude residue (0.75 g, 2.16 mmol), BOP reagent (1.05 g, 2.38 mmol) and potassium hydrogen carbonate (1.08 g, 10.8 mmol)
- are dissolved in 20 mL of DMF. The reaction mixture is stirred for 16 hours and then diluted with 300 mL of EtOAc. The organic layer is washed with 1 N HCl, 10% Na₂CO₃ and saturated NaCl. The organic layer is dried over MgSO₄, filtered and concentrated. The residue is purified by column chromatography eluting with a gradient of 15% EtOAc/CH₂Cl₂ to 35% EtOAc/CH₂Cl₂ to give the
- 10. stitle compound (0.26 g, 0.76 mmol) as a solid. 14 NMR (CDCl₃, 300 MHz) δ 7.49 (m, 4H), 5.50 (bs, 1H), 4.59 (s, 2H), 4.08 (m, 1H), 3.21 (m, 2H), 2.48 (m, 1H), 1.89 (m, 2H), 1.62 (m, 1H), 1.45 (s, 9H).
 - B. Naphthalene-2-sulfonic acid [1-(3-cyanobenzyl)-2-oxopiperidin-3-yl]amide.
- 15 3-[(N-Boc)-3-amino-2-oxopiperidin-1-ylmethyl]-benzonitrile (0.25 g, 0.76 mmol) is dissolved in 5 mL of CH₂Cl₂. To the solution is added 1 mL of trifliporteacetic acid. The mixture is stirred for 3 hours at room temperature and then
- concentrated. The residue is reconcentrated from toluene to give 3-(3-amino-2-oxopiperidin-1-ylmethyl)benzonitrile trifluoroacetate (0.23 g, 0.76 mmol) as a
- 20 g solida The crude product is then treated as in EXAMPLE 1, Part D to give the
- 300 MHz) δ 8.49 (s, 1H), 7.94 (m, 4H), 7.51 (m, 6H), 6.10 (s, 1H), 4.47 (AB, 2H); 3.56 (m, 1H), 3.20 (m, 2H), 2.52 (m, 1H), 1.83 (m, 3H).
- 25 <u>C!! Naphthalene-2-sulfonic acid (1-[3-(aminoiminomethyl)benzyl]-2-</u>

The title compound is prepared as in EXAMPLE 1, Part E using naphthalene-2-sulfonic acid [1-(3-cyanobenzyl)-2-oxopiperidin-3-yl]amide as the starting material by a singular residual to the starting

¹H.NMR (DMSO-d_e, 300 MHz) δ 9.29 (bs, 2H), 9.19 (bs, 2H), 8.48 (s, 1H), 8.04 (m, 4H), 7.90 (d, 1H), 7.60 (m, 6H), 4.48 (s, 2H), 3.95 (m, 1H), 3.18 (s. 2H), 1.86 (m, 1H), 1.69 (m, 3H). FAB MS, [M+H] = 437. Elemental analysis calculated with 1 mole of H₂O: C=52.81%, H=4.79%, N=9.84%, found

The filth compound is prepared as in EXAMPLE 1, Pay LES administration of the endoughous statements and the endoughous statements and the endoughous statements are the endoughous statements.

ு நகுக் <u>7-Methoxynaphthalene-2-sulfonic acid (1-[3-(aminoiminomethyl)benzyl]-2-oxo-</u> காருக் **azepan-3-(S)-vl)amide trifluoroacetate** நடிகை கடிக்கள் குகிக்கி

out hine. A portion of the crude residuar (0.1.3 μ , 2.13 mmof), BOP μ , $\mu_{\rm c}$ μ (1.05 μ , 2.38 mmof) and $\mu_{\rm c}$ $\mu_{\rm c}$ mathematical ending 208 mmof).

ı i

- L-(-)-α-Amino-ε-caprolactam (5 g₁39 mmol) and triethylamine (4.9 g, 49 mmol) are dissolved in 100 mL of CH₂Cl₂ ato the solution is added Boc annychide (8.5 g, 39 mmol) and dimethylaminopyridine (0.1 g). The reaction mixture is stirred for 16 hours at room temperature. After this time, the solution is washed with 1 N HCl, 10% Na₂CO₃ and saturated NaCl. The organic layer is dried over 10 MgSO₄, filtered and concentrated to give the title compound (6.23 g) 27 mmol) as a solid. He add 0.3 d (HA mg 9) 10 mmol (HA NMR (CDCl₃ 300 MHz) 8.6.15 (bs, 1H), 5.90 (bs, 1H); 4:24 (m, 1H), 3.21 (m, 2H), 2.05 (m, 2H), 1.79 (m, 2H), 1.45 (m, 11H).
- 15 B. [1-(3-Cyanobenzyl)-2-oxoazepan-3-(S)-yl]carbamic acid tert-butyl ester.

 L-(-)- α-Boc-amino-ε-caprolactam (1.07 g, 4.7 mmol) is dissolved in 45 mL of THF and cooled to 0°C. To the solution is added a 1M solution of lithium hexamethyldisilylazide (4.7 mL, 4.7 mmol) in THF. The mixture is stirred for 30 minutes at 0°C. To the resulting solution is added α-bromo-m-toluyl nitrile (0.9)
- g, 4.7 mmol). The reaction mixture is stirred for 4 hours. The solution is diluted with 100 mL of EtOAc and is washed with 1 N HCl, 10% Na₂CO₃ and saturated NaCl. The organic layer is dried over MgSO₄; filtered and concentrated. The residue is purified by column chromatography eluting with 20% EtOAc/CH₂Cl₂ to give the title compound (1.05 g, 3.1 mmol) as a solid.
- 25 ¹H NMR (CDCI₂, 300 MHz), δ, 7.45 (m, 4H), 5.95 (d, 1H), 4.85 (AB(1H), 4.35 (AB, 1H), 4.40 (m, 1H), 3.48 (m, 1H), 3.15 (dd, 1H), 2.05 (m, 1H), 1:90 (m, 1H), 1.70 (m, 2H), 1.49 (m, 1H), 1.45 (s, 9H), 1.20 (m, 1H), 1.60 (m,

cole out on the elly-6-monarchoxe-6-(lyanudaness-7) 1) bias alnohus.

C. 3-(3-(S)-Amino-2-oxoazepan-1-ylmethyl)benzonitrile hydrochloride.

- The title compound is prepared as in EXAMPLE 1, Part C using [14(3-1 cyanobenzy])-2-oxoazepan-3-(S)-yl]carbamic acid tert-butyl ester as the starting material. EI MS, [M] +=243. http://discrete.com/miles/ester/
 - D. 7-Methoxynaphthalene-2-sulfonic acid [1-(3-cyanobenzyl)-2-oxoazepan-3-(S)-yl]amide.

The title compound is prepared as in EXAMPLE 1, Part D using 3-(3-(S)-amino-2-oxoazepan-1-ylmethyl)benzonitrile hydrochloride and

7-methoxynaphthalene sulfonyl chloride as the starting materials.

¹H NMR (CDCl₃, 300 MHz) δ 8.32 (s, 1H); 7.88 (m, 2H), 7.68 (d, 1H), 7.29 (m, 3H), 7.08 (m, 1H), 6.96 (m, 1H), 6.35 (d, 1H), 4.80 (AB, 1H), 4.10 (AB, 1H), 4.00 (m, 1H), 3.92 (s, 3H), 3.19 (m, 1H), 3.05 (m, 1H), 2.18 (m, 1H), 1.95 (m, 1H), 1.65 (m, 2H), 1.18 (m, 3H).

E. 7-Methoxynaphthalene-2-sulfonic acid (1-[3-(aminoiminomethyl)bengyl]-2-oxoazepan-3-(S)-yl\amide trifluoroacetate.

15 3H), 1:12 (m;:1H). FAB MS, [M+H]*=4819 Elemental analysis calculated with 0.5 mole of H₂O:: C=53.73%, H=5.01%; N=9.28%, found C=53.77%, H=4.86%, N=9.26%. The transfer of the control of the control

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20 <u>7-Methoxynaphthalene-2-sulfonic acid {1-[3-(aminoiminomethyl)herzytte oxopyrrolidin-3-(S)-yl}methyl amide trifluoroacetate.</u>

அத்த ச<mark>ி.க. 7-Methoxynaphthalene-2-sulfonic acid [1-(3-cyanobenzyl)-2-oxopyrrolidin-</mark> கத்தே 3-(S)-yl]methyl amide வு.கே. இக்கி விள்ள முயின்-மு.ன். மி.க. Dr.a (நார்க்

- The title compound disprepared as in EXAMPLE 17, Part A⁽¹⁾ sing 7methoxynaphthalene-2-sulfonic acid [1-(3-cyanobenzyl)-2-οχορŷrrolidin-3-(S)yl]amide as the starting material are an element to the bewolfs ¹H.NMR (CDCl₃, 300 MHz) δ 8.44 (d, 1H), 7.92 (d, 1H), 7.82 (m, 2H), 7.61 (m, 1H), 7.47 (m, 3H), 7.28 (m, 2H), 4.97 (m, 1H), 4.53 (AB; 1H), 4.39 (AB, 1H), 3.96 30 (s, 3H), 3:13 (m, 2H), 2:83 (s, 3H), 2:36 (m, 1H), 2:37 (m, 1H), 2.06 (m, 1H).
 - ் Bor7-Methoxynaphthalene-2-sulfonic acid-(1-[3-(aminoiminomethyl)hen:யி-2oxopyrrolidin-3-(S)-yl}methŷl amide trifluoroacetate. இது நடுக்கும்
 - The title compound is prepared as described in EXAMPLE 1, Part E using 7-methoxynaphthalene-2-sulfonic acid [1-(3-cyanobenzyl)-2-oxopyrrolidin-3-(S)-yl]methyl amide as the starting material.

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¹H.NMR₂ (DMSO₂d₆, 300 MHz) δ.9.28 (bs, 2H) σ.9.07 (bs, 2H) δ.8.38 (s, 1H), 8.01 (d, 1H) σ.7.93 (s, 1H), σ.68 (m, 2H) ε7.54 (m; 4H), σ.33 (d; 1H), 4.90 (m, 1H), 4.40 (H) ε (AB, 2H), 3.88 (s, 3H), 3.12 (m, 2H); 2.66 (s, 3H), 9.8 (m, 1H), 1.75 (m, 1H). (h) ε (AB, 2H), 3.88 (s, 3H), 3.12 (m, 2H); 2.66 (s, 3H), 9.80 (m, 1H), 1.75 (m, 1H). (h) ε (AB, 2H), 1.88 (s, 3H), 3.12 (m, 2H); 2.66 (s, 3H), 9.10 (m, 1H), 1.75 (m, 1H). (h) ε (AB, 2H), 1.88 (s, 3H), 3.12 (m, 2H); 2.66 (s, 3H), 1.98 (m, 1H), 1.75 (m, 1H). (h) ε (AB, 2H), 1.88 (s, 3H), 3.12 (m, 2H); 2.66 (s, 3H), 1.98 (m, 1H), 1.75 (m, 1H). (h) ε (AB, 2H), 1.88 (s, 3H), 3.12 (m, 2H); 2.66 (s, 3H), 1.98 (m, 1H), 1.75 (m, 1H). (h) ε (AB, 2H), 1.88 (s, 3H), 1.98 (m, 1H), 1.75 (m, 1H), 1.75 (m, 1H), 1.88 (s, 3H), 1.88 (s, 3H

3-(3-(S)-Amino-2-oxopyrrolidin-1-ylmethyl)benzönitrile hydrochloride.

voolts and group and an experience of European at European at European at European at European at European at European Application of (S)-yl)-carbamic acid: tert-butyl ester. Its of the solution of (S)-Boc-diaminobutyric acid (25 g):115 mmol), triethylamine (HT a (35 g, 344 mmol)) and hydroxybenzotriazole (19.3 g, 443 mmol) in 0.5 L of THF (HT b) or is added, 1:(3-dimethylaminopropyl)-3-ethylcarbodiimide (hydrochloride (27.4 g, 1) to 1143 mmol). The solution is heated to 60°C over 15 minutes. A white of 15. precipitate forms and the solution is kept at 60°C for 4 hours? After this time, the solution is filtered and the collected liquid is concentrated. The crude product

solution is filtered and the collected liquid is concentrated. The crude product is purified by column chromatography in a gradient of 1% MeOH/CH₂Cl₂ to 3% MeOH/CH₂Cl₂ to afford the title compound (19.6 g, 98 mmol) as a white solid.

1H NMR (CDCl₃, 300 MHz) δ 6.17 (bs, 1H), 5.08 (bs, 1H), 4.12 (m,41H), 3.33 (m,

20:2H), 2.65; (m_{0.1}H), 2.00) (m; 1H), 1.42; (s), 9H), englaging an excitation of the content of the cont

B. [1-(3-Cyanobenzyl)-2-oxopyrrolidin-3-(S)-yl]carbamic acid tert-butyl ester.

Το a solution of (2-oxopyrrolidin-3-(S)-yl)-carbamic acid tert-butyl ester (9 g, 45 mmol) and α-bromo-m-toluyl nitrile (9.3 g, 47 mmol) in 225 mL of THE/DMF

25 (10:1) at 0°C is added a 60% mineral oil dispersion of sodium hydride (1.8 g, (3) and (46 mmol). The reaction mixture is stirred at 0°C for 0.5 hours and then is allowed to warm to ambient temperatures #After 3 hours, the reaction mixture is quenched by the addition of saturated NH₄Cl and diluted with EtOAdd The layers are separated. The organic layer is washed with 1 N HCl, H₂O and

30 saturated NaCl., The organic layer is dried over MgSO₄, filtered and concentrated. The crude product is purified by column chromatography eluting with gradient of 20% EtOAc/hexanes to 40% EtOAc/hexanes to afford the title compound (12.7 g, 40 mmol) as a white solid ratio (2) Solid 11 mm (CDCl₃, 300 MHz) δ 7.55 (m, 4H), 5.18 (bs, 1H), 4.47 (AB, 2H), 4.18

(dd, 1H), 3.21 (m, 2H), 2.60 (m, 1H), 1.42 (s, 9H), seen respect to the control of the control o

Johnson printiste entra abina tyra, may-(3)

C. 3-(3-(S)-Amino-2-oxopyrrolidin-1-ylmethyl)benzonitrile hydrochloride.

To a solution of [1-(3-cyanobenzyl)-2-oxopyrrolidin-3-(S)-yl]carbamic and tentbutyl ester (9.1 g, 29 mmol) in 150 mL of EtOAc at 0°C is bubbled HCl gas for 10 minutes. After this time, the solution is stirred for 4 hours. The solution is then concentrated to give the title compound (7.3 g, 29 mmol) as a white solid.

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¹H NMR (DMSO-d_s, 300 MHz) δ 8.71 (bs, 3H), 7.85 (m, 2H), 7.70 (m, 2H), 4.58 (AB, 2H), 4.13 (m, 1H), 3.32 (m, 2H), 2.44 (m, 1H), 2.18 (m, 1H).

EXAMPLE 24

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6-Methoxynaphthalene-2-sulfonic acid (1-13-(aminoiminomethyl)benzyl]-2oxopyrrolidin-3-(S)-vl}amide trifluoroacetate.

A : 6-Methoxynaphthalene-2-sulfonyl chloride.

Short Filter J. governor (2.18 g. 0.4), novel to shirt

James B. W. St. C.

To a suspension of 6-hydroxynaphthalene-2-sulfonic acid, sodium salt (5 g, 20.3 mmol) in 40 mL of 2:1 H₂O/ethanol Is added solid NaOH (0.89 g, 22.3

- mmol) at room temperature. The resulting black mixture is stirred until a 15 homogenous solution forms, and dimethyl sulfate (2.11 mL, 22.3 mmol) is then added. The mixture is stirred over a period of 16 hours as a precipitate eventually forms. The crude mixture is concentrated in vacuo and the residue e is stirred in 70 mL of absolute EtOH as a slurry. The precipitate is filtered and
- 20 m dried. The solid is heated at reflux in 100 mL of 95% EtOH for 2.5 hours allowed to cool to room temperature; filtered and dried to give 3.31 g of crude 6-methoxynaphthalene-2-sulfonic acid, sodium salt. A mixture of the sulfonic acid; sodium salt (3:31 g, 12.7 mmol) in 5:3 mL of phosphorous oxychloride candaphosphorous pentachloride (3:44 g, 16:5 mmol) is heated slowly to 60°C
- 25 untilia homogenous solution forms and then is heated at 120°C for 4 hours. The resulting mixture is allowed to stir at room temperature overnight, then is
- Added slowly to a mixture of ice/ice water. The mixture is diluted with water and extracted with CHCI. The combined organic layers are washed Chia successively with water and saturated NaHCO3 solution. The organic phase is
- dried over anhydrous MgSO4, filtered and concentrated to give 4 g of a crude product. The crude product is purified by column chromatography in a gradient of 10% EtOAc/hexanes to 20% EtOAc/hexanes to afford the title compound
 - 35 n.1H), 3:99 (ŝ; 3H). ÉLIMS, [M] ♣256. ்டுள் சென்ன கிரியை விளியவிற்

Service V 30% Harrish Neo Neo 19%

B. 6-Methoxynaphthalene-2-sulfonic acid [1-(3-cyanobenzyl)-2-oxopyrrolidinbudyi ester (9.1 g. 29 minot) in 150 mL of EICAG at ablamble (9.1 g. 128) rates iyibd Secondary 3-(3-(S)-Amino-2-exopyrrolidin-1-ylmethyl)benzonitrile hydrochloride (0.20 g, To the solution is added وراكر عنارين وراكر 10 mL of CH 23. (5g., triethylamine (0.24 g., 2.37 mmol) followed by 6-methoxynaphthalene-23 sulfonyl chloride (0.25 g, 0.99 mmol). After stirring for 1.5 hours the solution is diluted with EtOAc and washed with 1 N aqueous HCl, water, saturated NaHCO_a solution and saturated NaCl solution. The organic laver over MgSO4 filtered and concentrated to provide crude material which is purified by column chromatography in a gradient of 20% EtOAc/ CH, Clato 50% EtOAc/CH₂Cl₂ to afford the title compound (0.18 g, 0.41 mmol) as a solid. ¹H NMR (CDCl₃, 300 MHz) δ.8.40 (s, 1H), 7.90 (m, 3H), 7.59 (m, 1H), 7.46 (m, (m, 3H), 7,29 (m, 1H), 7,20 (d, 1H), 5.40 (d, 1H), 4.40 (s, 2H); 3,99 (s, 3H), 3.75 (m, SS . n 1H) 03.20 (m, 2H), 2.60 (m, 1H), 2.13 (m, 1H) to Jm 04 ni (lourin & DS in in all at room temperature. The resulting black mixture is stirred until 21 13-6-Methoxynaphthalene-2-sulfonic acid-(1-[3-(aminoiminomethyl)benzyl]-2ens oxopyrrolidin-3-(\$)-yl]amide trifluoroacetate. A ensistent entre padde LITE TO STATE (S)-yllamide (0.18 g, 0.41 mmol): is dissolved in 10 mL of a 2:1 mixture of 20 EtOH/CH₂Cl₂: The solution is cooled to 0°C and HCl gas is bubbled through the solution for 10 minutes. The ice bath is removed and the reaction mixture is stirred at room temperature for 18 hours. After this time the solution is soncentrated and pumped; under high vacuum until dry. ir The residue is Cold of ydissolved in 10 mL of methanol, cooled to 0°C and ammonia gas is bubbled 25 through the solution for 10 minutes. The reaction mixture is stirred at room temperature for 42 hours. After this time, the solution is concentrated and the residue is purified by RR-HPLC eluting with a gradient of 10% CH₂CN/H₂O (0.1% TFA) to 60% CH₃CN/H₂O (0.1% TFA) over a 30 min period.bThe appropriate fractions are lyophilized to give the title compound (0.11.g, 0.19 mmol) as an amorphous white solid. If LOSDM sucributing revolution ¹H NMR (DMSO-d₆, 300 MHz) δ.9.30 (bs. 2H), 9.10 (bs. 2H), 8.40 (s. 1H), 8.19 'तानांधाराध्य हा (d, 1H), 8.04 (d, 1H), 8.00 (d, 1H), 7.82 (dd, 1H), 7.68 (m, 1H), 7.55 (m, 3H), 7.45 (d, 1H), 7.30 (dd, 1H), 4.42 (AB; 2H), 4.15 (m, 1H) 3.91 (s; 3H), 3.09 (m, 2H), 1.99 (m, 1H), 1.58 (m, 1H). FAB MS; [M+H] =453! Elemental analysis

calculated with 2.5 mole of H₂O: C=50.60%, H=5.13%, N=9.45%; toung

C=50.66%, H=4.28%, N=9.13%.

EXAMPLE 25

6-Methoxynaphthalene-2-sulfonic acid (1-[3-(aminoiminomethyl)benzyl]-2-oxopyrrolidin-3-(S)-yl)methyl amide trifluoroacetate.

- s i a j log matecal desperated for men applie (sential justice)。 A. 6-Methoxynaphthalene-2-sulfonic acid {1-(3-cyanobenzyl)-2-oxopyrrolidin-3-(S)-yl}methyl amide: 6 o h hyvat se Nelvariazon. O 61 1941 A 6-Methoxynaphthalene-2-sulfonic acid [1-(3-cyanobenzyl)-2-oxopyrrolidin-3-(S)-yl]amide (0.24 g, 0.55 mmol) is dissolved in 5 mL of an 8:1 mixture of THF/DMF and cooled to 0°C. Sodium hydride (24 mg of a 60% dispersion in 10 mineral oil, 0.61 mmol) is added and the solution is stirred for 15 minutes. To the mixture is added methyl iodide (0.15 g, 1).10 mmol). The cooling bath is removed and the solution is stirred at room temperature for 2 hours. The solution is poured into a separatory funnel and diluted with 100 mL of EtOAc. The organic layer is washed with 1 N HCI, saturated NaHCO, and saturated 15 NaCl, then dried over MgSO, filtered and concentrated. The crude residue is purified by column chromatography eluting with 25% EtOAc/CH, Cla to give the title compound (0.23 g, 0.51 mmol) as a solid. ¹H NMR (CDCl₃, 300 MHz) δ 8.45 (s, 1H), 7.87 (m, 3H), 7.59 (m, 4H), 7.20 (m, 2H), 4.95 (m, 1H), 4.44 (AB, 2H), 3.95 (s, 3H), 3.21 (m, 2H), 2.80 (s, 3H), 2.40 20 _ (m, 1H), 2.09 (m, 1H), (c) 3-millioning
 - ox 1946 B. 6-Methoxynaphthalene-2-sulfonic ácid (1-[3-(amiñóiminomethyl)benzyl]-2oxopyrrolidin-3-(S)-yl)methyl amide trifluoroacétate (1900 entire) via
 - The title compound is prepared as described in EXAMPLE 24, Part C using 625 methoxynaphthalenes2 sulfonic acid [1-(3-cyanobenzyl)-2-oxopyrrolidin-3-(S)yl]methyl amide as the starting material. The imidate intermediate is formed over a period of 18 hours at room temperature. The amidine formation occurred over a period of 18 hours at room temperature. The crude product is purified by RP-HPLC eluting in a gradient of 10% CH3CN/H3O (0.1% TFA) to

the promote state of the promote dissolution of the promote that it

- 35 த 3H), 2.00 (mg H)த1.79 (m, 4H) NFAB MS, [M+H] = 467. Elemental analysis calculated with 1.8 mole of H₂O ா C = 50.91%, H = 5.04%, N = 9.13%, found C = 50.92%, H = 4.55%, N = 8.83%, find patrongeness bos bereith. இதில்

ELLAPINE 25

2-[(1-[3-(Aminoiminomethyl)benzyl]-2-oxopyrrolldin-3-(S)-ÿl)-6-9-20 methoxynaphthalene-2-sulfonylamino]-N-phenethylacetamide trifluoroacetate.

ق <u>كَ كَا كَ الْمُعَانِمِينَ عَلَى 5-الْمُعَانِمِينَ عَلَى 5-الْمُعَانِمِينَ عَلَى 5-الْمُعَانِمِينَ عَلَى 5-الْمُعَانِمِينَ عَلَى 5-1{1-(3-Cyanobenzyl)-2-oxopyrrolidin-3-(2)-زاله-1-(3-Cyanobenzyl)-2-معنون على 4-[S-Light Sulfonylamino]-N-acetic acid t-butyl ester على عاداً المعالمة المعالم</u>

To a solution, of 6-methoxynaphthalene-2-sulfonic acid [1-(3-cyanobenzyl)-2-

10 (0.33 g, 0.76 mmol) and t-butyl bromoacetate (0.15 g; 0.77 mmol) in DMF risci (6 mL) is added K2COs (0.21 g, 1)5 mmol) (nThe reaction mixture is stirred for add 3 hours After this time, the reaction mixture is diluted with EtOAc and H₂C.

The layers are separated. The organic layer is washed with: H₂O and saturated NaCl. The crude product is purified by column chromatography in a gradient of 10% EtOAc/CH₂Cl₂ to 20% EtOAc/CH₂Cl₂ to afford the title compound (0.42 g.

purified by a Jumn chromatography alutamach etides a selic.

Strippound (0.23 g. 0.51 mmob as a selic.

mi) 02.7 B. 2-[(1-(3-Cyanobenzýl)-2-őxópyírőlidin-3-(5)-ýl)-6-methőxyírállári-1-2-2-2-2-2-(H.sulfonylaminol-N-acetic/acid.e) 3.95 (H.S. (AB. 34) 4.44 (AB. 34) 4.95 (H.S. (BB. 34) 4.95 (BB. 34) 4.95

20 2-[{1-(3-Cyanobenzyl)-2-oxopyrrolidin-3-(S)-yl}-6-methoxynaphthalene-2-sulfonylamino]-N-acetic acid t-butyl ester is dissolved in 25 mL

CH₂CI₂/trifluoroacetic acid₃(5:1). After 3: hours; the solution is concentrated to give the title compound as a white foam. ivdicatily (2) & nibiliouvaces:

1H,NMR, (CDCI₃, 300 MHz) 8.8.39 (s, 1H), 7.85 (m; 3H), 7.60 (d; 1H); 7.49 (m, 25). 3H), 7.19 (m, 2H), 4.77 (t, 1H), 4.51 (AB, 2H), 4.02 (m; 1H), 3.92 (s; 3H), 3.32

yimetryl amide ac ib.(Hta,m) [11.5; (Htp.m) i86.5; (HS,m) 88.6; (Ht.m) crined over a period of 13 incurs at room emperature. The amiding throughout

methoxynaphthalene-2-sulfonylamino]-N-acetic acid (0.41 gi 0.83 mmol), triethylamine (0.28 gi, 2.8 mmol) and phenethylamine (0.28 gi, 2.8 mmol) in 8 mL of DMF is added benzotriazol-1-yloxy-tris(dimethylamino)phosphonium hexafluorophosphate (0.37 gi, 0.83 mmol). The solution is stirred for 16 hours. After this time, the solution is diluted with EtOAce The organic layer is washed

with 1 N HCl, 10% Na₂CO₃ and saturated NaCl. The organic layer is washed MgSO₄, filtered, and concentrated. The crude product is purified by column

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chromatography eluting with gradient of 10% EtOAc/CH2Cl2 to 20% EtOAc/CH₂Cl₂ to afford the title compound (0.40 g, 0.70 mmol) as a white solid. 1 H NMR (CDCl₃, 300 MHz) δ 8.38 (s, 1H), 7.86 (m, 4H), 7.51 (m, 4H), 7.19 (m, 6H), 4.58 (AB, 1H), 4.38 (m, 3H), 3.91 (m, 3H), 3.78 (AB, 2H), 3.29 (m, 4H), 2.62 (m, 2H), 2.21 (m, 2H). Application of the second se

Tark to main wild breching to D. 2-[(1-[3-(Aminoiminomethyl)benzyl]-2-oxopyrrolidin-3-(S)-yl}-6methoxynaphthalene-2-sulfonvlamino]-N-phenethylacetamide trifluoroacetate. The title compound is prepared as described in EXAMPLE 24, Part C using 2-10 [{1-(3-cyanobenzyl)-2-oxopyrrolidin-3-(S)-yl}-6-methoxynaphthalene-2sulfonylamino]-N-phenethylacetamide as the starting material. The crude product is purified by RP-HPLC eluting in a gradient of 10% CH₂CN/ H₂O (0.1% TFA) to 60% CH₃CN/H₂O (0.1% TFA) and the appropriate product fractions are lyophilized to provide the title compound as a white solid. 2 10 m ¹H NMR (DMSO-d₆, 300 MHz) δ 9.30 (bs, 4H), 8.48 (s, 1H), 8.19 (m, 1H), 8.00 (m, 2H), 7,88 (m, 1H), 7.69 (m, 1H), 7.54 (m, 3H), 7.42 (m, 1H), 7.18 (m, 5H), 4.80 (f, 1H), 4.41 (m, 2H), 3.89 (m, 4H), 3.56 (m, 1H), 3.18 (m, 4H), 2.62 (m, 2H), 2.01 (m, 2H). FAB MS, [M+H]*=614. Elemental analysis calculated with 2.25 mole of H₂O cal. C=54.90%, H=4.79%, N=9.01%, found C=54.72%, H=5.31%,

a pure de de la brance de la company de la c complete with our liberal common to be held to seve 9.10-Dioxo-8a.9.10.10a-tetrahydroanthracene-2-sulfonic acid (1-13-) (aminoiminomethyl)benzyl]-2-oxopyrrolidin-3-(S)-yl)amide_trifluoroacetate.

N=9.12%. SMAXE SET TO FOR THE STARTE SET SET AND SET OF THE SECRET OF TH

thiles at two as bouldomes all should ask a to 24 A.: Anthraguinone-2-sulfonyl-chlorides (2HM 008 ab-O2MQ) 540 1 H A mixture of anthraquinone-2-sulfonic acid, sodium salt) (5 gr 15.2 mmol) in 6.4 mL of phosphorous oxychloride and phosphorous pentachloride (4.12 g. 19.8 mmol) is heated slowly to 60%C until a homogenous solution forms and then is heated at 120°C for 4 hours. The resulting mixture is cooled in an ice bath and a mixture of ice/ice water is added slowly with stirring. The mixture is diluted with water and extracted twice with CHCl_a. The combined organic layers are washed successively with saturated NaHCO solution and saturated NaCI solution. The organic phase is dried over anhydrous MgSO filltered and concentrated to give 4.50 g of crude product sulfonyl chloride which is of 38

35 sufficient purity to be used in subsequent reactions and Translation &

The the compound is propromised to described in EXAMPLE 24, Plus 4 Aurign

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JH)NMR (CDCl<sub>3</sub>/300 MHz) δ 8.99 (d, 1H), 8.58 (d, 1H), 8.39 (m, 3H), 7.90 (m,
 tites etiny 2H). EI MS, (M]+=306.0) britis con etit ent biotia of ,HO,HO\chies
  'H NMR (CDCl<sub>a</sub>, 300 MHz) 5 €.38 (s, 1H), 7.85 (m, 4H), 7.51 (m, 4H), 7.19 (m,
30 - 14 m B. 9.10-Dloxô-8a.9.10.10a-tetrahvdroanthracehe-2-sulfonio
            cyanobenzyl), 2.21 (ra, 2H), abimafly-(S)-vilamide, (HS, ra) (12.21), 2.21
            The title compound is prepared from 3-(3-(S)-amino-2-oxopyrrolidin-1-
            ylmethyl)benzonitrile hydrochloride as in EXAMPLE 24. Part Busing
 ວ່າຮ່ອງກາວງເວລກthraquinone+2-sulfonyl chloride in place of 6-methoxynaphithalene-2-
 2 prote Osulfonyl chloride. The crude product is purified by column chromatography in a
      10 - gradient of 20% EtOAc/CH, Cl; to 40% EtOAc/CH, Cl; to give the title compound
      sulfanylamino]-N-phenergylacetamide as the starting matchlics a za crude
... ο ομιλήμ NMR (CDCl<sub>a</sub>:300 MHz) δ 8.82 (d, 1H), 8.41 (d, 1H), 8.30 (m, 3H), 7.85 (m,
 316 840000 2H) 27.58 (d, s1H) 77.47 (m, 3H) 6.20 (bs, 1H) 4.50 (AB, 2H) 4.03 (m, 1H), 3.29
            (m, 2H), 2.69 (m, 1H), 2.15 (m, 1H) noo ellit ent ebivora of bezilingay
  'H NMR (DMSO-de, 500 MHz) 8 8.30 (bs. 4H), 8.48 (s. 1H), 8.19 (m. 1H, 2L.30
    HE IM C. 9.10-Dioxo-8a.9/10.10a-tetrativdroanthracene-2-sulfonic acid (1-13-
(15 m) 30 (aminoiminomethyl)benzvil-2-oxopvirolidin-3-(S)-vilamide trifluoroacetate.
   마요 하시9/10/Dioxo-8a;9/10/10a-tetrahydroanthracene 2-sulfonic acid [1-(3-
Cyanobenzyl)-2-oxopŷrrolidin-3-(S)-ŷl]amide îs converted to the title compound
            as described in EXAMPLE 24, Part C. The imidate intermediate is formed over
            a period of 18 hours at room temperature. The amidine formation accurred
            over a period of 18 hours at room temperature. The crude product is purified
            by RP-HPLC eluting in a gradient of 10% CH CN/H, O (0.1% TFA) to 60%
     CH, CN/H2O (0.1%: TFA) and the appropriate product fractions are lyophilized to
            provide the title compound as a white solid.
            <sup>1</sup>H NMR (DMSO-d<sub>6</sub>, 300 MHz) δ 9:28 (bs) 2H); 9.05 (bs) 2H) 8:63 (d, 1H), 8.59
 al (lo. (d. 1H); 8,32)(m; 2H); 8.20 (m; 2H); 7.94 (m); 2H); 7.61 (m, 1H); 7.50 (m, 3H).
  5.03 (AB, 2H), 4:21:(m):1H); 3.08!(m):2H); 2:09 (m):1H); 1:60 (m):1H). FAB MS.
  ાં લાકામાં કું કુંકામાં કું કુંગુલા Elemental analysis calculated with 1.8 mole of H Ö: C≌51.78%,
 ு 30.4 H=4/14%(N=8.63%) found: C=51.79%, H≛3.82%(N=8.28%) S कि कि कि
    a mixture or ice/ice water is added slowly with stirring. The mixture is diluted
   will water and extracted twice with CHOL. The combines algunaxa errale
      ுதமு8-Chloro-7-methoxynaphthalerie-2-sulfonic acid 141-13- உரும் மா berterw
       aminoiminomethyl)benzyll-2-oxopyrrolidin-3-(S)-yllamide trifluoroacetate.
     sense thated to give 4.50 g of clude product sulfant chloride which is of 36
           A. 8-Chloro-7-methoxynaphthalene-2-sulfonvt chloride: thing first and
           The title compound is prepared as described in EXAMPLE 24, Part A using
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7-hydroxynaphthalene-2-sulfonic acid, sodium salt (15 g, 60.9 mmol) in place of 6-hydroxynaphthalene-2-sulfonic acid, sodium salt. The crude 7methoxynaphthalene-2-sulfonic acid, sodium salt (12.6 g) obtained is likewise chlorinated in the presence of excess phosphorous oxychloride and phosphorous pentachloride. The crude product (10 g) is purified by column chromatography in a gradient of 5% EtOAc/hexanes to 30% EtOAc/hexanes to afford the title compound (1.49 g, 5.12 mmol) as the minor component as a solid, remone remove the states amade solves their contact of the ¹H NMR (CDCl₃, 300 MHz) δ 8.95 (d, 1H), 8.01 (d, 1H), 7.90 (d, 2H), 7.55 (d,

1H), 4.09 (s, 3H). El MS, [M]+=290.

The 7-methoxynaphthalene-2-sulfonyl chloride (3.80 g; 14.8 mmol) is also isolated as the major component from the above procedure as a white crystalline solid-ladoromivnismo, delw deblert a notuloc en C. 200 -

¹H NMR (CDCl₃, 300 MHz) δ 8,49 (d,:1H), 7.96 (d,:1H), 7.85 (d,:2H), 7.39 (dd,

at he local neithbor betceron edf. shield to be the digmon benefit he is that in B. 8-Chloro-7-methoxynaphthalene-2-sulfonic acid [1-(3-cyanobenzyl)-2oxopyrrolidin-3-(S)-yl]amide.log. Htt Dorda in the Challes of their

The title compound is prepared from 3-(3-(S)-amino-2-oxopyrrolidir)-1ylmethyl)benzonitrile hydrochloride as in EXAMPLE 24. Part B using 8-chloro-7-methoxynaphthalene-2-sulfonyl chloride in place of 6-methoxynaphthalene-2-sulfonyl chloride. The crude product is triturated from 50% EtOAc/hexanes solution to give the title compound as a beige solid xoling without the // 'H NMR (CDCl_a, 300 MHz) δ 8.81 (s; 1H), 8.00 (d; 1H), 7.86 (m; 2H), 7.59 (m,

25 (m, 4H), 7.45 (m, 4H), 5.49 (s, 1H), 4.47 (s, 2H), 4.10 (s, 3H)? 3.81 (m, 1H), 3.22 (m, ு நடி 2H); 2,65 (m; 4H); 2,40 (m, 4H), rim 08 rui செர்வுகை வரை fa benus of a 20% often actu/water columns. The resulting mixture is poured after

C. 8-Chloro-7-methoxynaphthalene-2-sulfonic acid (1-[3-] VIOLENE 198 (aminoiminomethyl)benzyl]-2-oxopyrrolidin-3-(S)-yl)amide trifluoroacetate.

30 8-Chloro-7-methoxynaphthalene-2-sulfonic acid [1-(3-cyanobenzvi)-2oxopyrrolidin-3-(S)-yllamide is converted to the title compound as described in EXAMPLE 24, Part C. The imidate intermediate is formed over a period of 18 hours at room temperature. The amidine formation occurred over a period of 18 hours at room temperature: The crude product is purified by RP-HPLC

eluting in a gradient of 10% CH₃CN/H₂O (0.1% TFA) to 60% CH₃CN/H₂O (0.1% 35 TFA and the appropriate product fractions are lyophilized to provide the title compound as a white solid.

2. 210 61 0 cH NMR (DMSO-da; 300 MHz) 8:9.35 (bs; 2H), 9:30 (bs; 2H), 8:66 (s, 1H), 8.41 -(de1H); 8:15 (d;相H); 8:10 (d;性H); 7:81 (dd,性H); 7:76 (d;性H); 7:68 (m, 1H), 7:55 11.60,(m;:1H).x:FAB MS; [M+H]*≘487? Elemental analysis calculated with 1 mole -m.500 of H₂O: C=48,54%; H=4,23%, N=9,06%; found C=48.53%, H=4.08%, N=8.72%. chromatography in a gradient of 5% EtOAc/hext.nrs to 20% EtOAc/hest tree to sford the little compound (1 44 g, 5.12 mnot) as the nee 319MAX2 or ps. a 7-Methoxynaphthalene-2-sulfonic acid (1-[4-(aminoiminomethyl)benzyl]-2-15) 38 roxopyrrolidin-3-(S)-vllamide triffüoroacetate M OVE , IODO, 130/V. In 1HJ, 4.09 (s, 3H) ELMS, (MJ+299). 10 The 7-methoxynaphtnalene-2-sulfonyl chloridanBO-(H)qaA-d-oBc-As also SI Boc-L-Asp-OBn (15:g/c46:4 mmol) is dissolved in 50 mL of THF and cooled to -10°C. The solution is treated with N-methylmorpholine (4.9 g, 48.7 mmol) and ு (சது stirred for 5 minutest) To the solution is added dropwise isobutyl chloroformate (6.3 g, 46.4 mmol). After the addition is completed; the solution is stirred for 1 minute, then filtered through a pad of Celite. The collected solution is cooled to -S-//v-10°C. To the solution is added sodium borohydride (2.63 g, 70 mmol) predissolved in 50 mL of water. The solution is stirred for 2 minutes. The solution is poured into a separatory funnel and diluted with 800 mL of EtOAc. 20. a The organic layer is washed with water and saturated NaCl. The organic layer sandis, dried, over-MgSO4 filtered and concentrated of The resulting residue is added to a solution of exalyl chloride (30 ml of a 2 M solution in CH2CI2 60 mmol), and methyl sulfoxide (7.25 g; 92.8 mmol) in 250 mile of CH2Cl2 at 178°C. The 80 Re reaction mixture is stirred at -78°C for 40 minutes, then triethylamine (14 g, 140 mmol) is added: The reaction mixture is stirred at 78°C for 1 hour and then is stirred at room temperature for 30 minutes. The solution is poured into 200 mL of a 20% citric acid/water solution. The resulting mixture is poured into ϵ separatory funnel and the layers are separated. The organic layer is washed with water, and saturated NaCl. The organic layer, is dried over MgSO4, filtered and concentrated. The residue is purified by column chromatography eluting with a gradient of 10% EtOAc/hexanes to 30% EtOAc/hexanes. The product EXAMPLE M. Part C. Jiorna ab annoil. O may M. BUSIMAXE 1H NMR (CDCI, 300 MHz) δ 9.68 (s.1H), 7.32 (m; 4H), 5.42 (bs; 1H); 5.16 (s. Our 2H), 4.62 (m, 2H), 3.05 (ddd, 2H), 1:40 (s; 9H) regmen moor is கல்லில் eluting in a gradient of 10% CHJONNA,O (0.1% YEAR to 80% CHJONNA for eluting

B. 11-(4-Cyanobenzyl)-2-oxopyrrolidin-3-(S)-yl]carbamic acid ren-butyl ester.

prompound as a white solid.

To a solution of Boc-L-Asp(H)-OBn (1.82 g, 5.93 mmol) dissolved in 30 mL of methanol is added p-cyanobenzylamine hydrochloride (1 g, 5.93 mmol) and triethylamine (0.66 g, 6.52 mmol). The solution is stirred for 45 minutes. After this time, a solution of sodium cyanoborohydride (0.41 g, 6.52 mmol) and zinc chloride (0.41 g, 3 mmol) in 6 mL of MeOH is added. The mixture is stirred for an additional 1.5 hours. After this time, 5 mL of 0.5 N NaOH and 10 mL of water is added, and the resulting mixture is concentrated. The residue is treated with 40 mL of water and 300 mL of EtOAc. The solution is filtered through a pad of Celite, poured into a separatory funnel and the layers are separated. The organic layer is washed with 1 N HCl, 10% Na₂CO₃ and saturated NaCl. The organic layer is dried over MgSO₄, filtered and concentrated. The residue is purified by column chromatography eluting with a gradient of 10% EtOAc/CH₂Cl₃ to 35% EtOAc/CH₂Cl₃ to give the title compound

15 ¹H NMR (CDCl₃, 300 MHz) δ 7.62 (d, 2H), 7.31 (d, 2H), 5.15 (bs, 1H), 4.53 (AB, 2H), 4.21 (m, 1H), 3.24 (m, 2H), 2.61 (m, 1H), 1.90 (m, 1H), 1.46 (s, 9H).

(0.67 g, 2.12 mmol) as a solid.

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25 D: 7-Methoxynaphthalene-2-sulfonic acid [1-(4-cyanobenzyl)-2-oxopyrrolidin-0.3-(S)-yllamide.

The title compound is prepared from 4-(3-(S)-amino-2-oxopyrrolidin-1-ylmethyl)benzonitrile hydrochloride as in EXAMPLE 24, Part B using 7-methoxynaphthalene-2-sulfonyl chloride in place of 6-methoxynaphthalene-2-sulfonyl chloride in place of 6-methoxynaphthalene-2-sulfonyl chloride. The crude product is triturated from EtOAc to give the title compound as a white solid.

1-(3-(S)-yllamide.

The title compound is prepared from 4-(3-(S)-amino-2-oxopyrrolidin-1-ylmethyl)benzonitrile hydrochloride as in EXAMPLE 24, Part B using 7-methoxynaphthalene-2-sulfonyl chloride in place of 6-methoxynaphthalene-2-sulfonyl chloride i

E. 7-Methoxynaphthalene-2-sulfonic acid {1-[4-(aminoiminomethyl)benzyl]-2-oxopyrrolidin-3-(S)-yl}amide trifluoroacetate.

7-Methoxynaphthalene-2-sulfonic acid [1-(4-cyanobenzyl)-2-oxopyrrolidin-3buy tom (\$)-yl]amide is converted to the title compound as described in EXAMPLE 24. Part C. The imidate intermediate is formed over a period of 18 hours at room temperature. The amidine formation occurred over a period of 18 hours at 5... room temperature o The crude product is purified by RP-HPLC eluting in agradient of 10% CH₃CN/H₂Q (0.1% TFA) to 60% CH₃CN/H₂Q (0.1% TFA) and the appropriate product fractions are lyophilized to provide the title compound treated with ±0 mL of water and 000 mL of EtOAcc. ⇒bilos stidus is an 1H NMR (DMSO-d₆, 300 MHz) δ 9,22 (bs, 2H), 9,18 (bs, 2H), 8.31 (s. 1H), ε.20 10 (d, 1H), 7.96 (d, 1H), 7.86 (d, 1H), 7.70 (d, 2H), 7.66 (dd, 1H), 7.49 (d, 1H), 7.34 (d, 2H), 7,28 (dd, 1H), 4,38, (AB, 2H), 4,10 (m, 1H), 3.82 (s, 3H), 23.03 (m, 2H), 8 (14 1.96 (m. 1H), 1.52 (m. 1H). ISP MS, [M+H]*=453. Elemental analysis calculated with 1.2 mole of H₂O: 60=51.09%, H=4.69%(N=9.53%, found C=51.09%, H=4.35%, N=9.31%. (0.67 g. 2.12 immol) as a solid. 11 NMR (CDCI₂, 300 MHz) 8 7.62 (d, 2H), 7.31 (a, 2H), 5.15 (bs, 1H) = .65 (b) EXAMPLE 30 (m) 14: (h) . 2.61 (m) 13: (h) . 3.0 (m) . 1.90 (m) . 1.90 (h) . 1.90 (h) . 1.90 (h) . 2.61 (h) . 3.00 (h) . 3 enting oxopyrrolidin-3-(S)-yl)amide trifluoroacetate. 2-2-101A-(E)-8-2-2-2 The title concound is prepared as a white suit from [1-(4-cyanoberz //1/2 A. 6.7-Dimethoxynaphthalene-2-sulfonyl chloride (8) 8-mail: https://doi.org/10.000 115 The title compound is prepared as in EXAMPLE 24, Part A using 4.89 6,7-dihydroxynaphthalene-2-sulfonic acid, sodium salt hemihydrats-in place of 6-hydroxynaphthalene,2-sulfonic acid, sodium salt. The crude product mixture is purified by column chromatography in a gradient of 10% EtOAc/hexanes to 30% EtOAc/hexanes to give the title compound as the major component. 85 1H), 4.09 (s, 3H), 4.07 (s, 3H), EI MS [M] = 286. Dayloumon with a T ylmethyl)berzonialle hydrophlorine as in EXAMPLE 24. Part Blustno 6.7-Dimethoxynaphthalene-2-sulfonic acid [1-(3-cyanobenzyl)-2-11 30 waternyl chlorice. The crude promist is (right and live chlorice). The title compound is prepared from 3-(3-(S)-amino-2-oxopyrrolidin-1ylmethyl)benzonitrile hydrochloride as in EXAMPLE 24, Part B using 6,7dimethoxynaphthalene-2-sulfonyl chloride in place of 6-methoxynaphthalene-2-sulfonyl chloride. The crude product is purified by column chromatoguaphy in 50% EtOAc/CH,Cl, to afford the title compound as a beige solid. 35

 $^{1}\text{H NMR (CDCl}_{3},\,300\,\,\text{MHz})\,\,\delta\,8.31$ (d, 1H), 7.81 (m, 2H), 7.59 (m, 1H), 7.45 (m, 3H), 7.20 (d, 2H), 5.39 (d, 1H), 4.48 (AB, 2H), 4.07 (s, 3H), 4.06 (s, 3H), 3.75 (m, 1H), 3.20 (m, 2H), 2.60 (m, 1H), 2.10 (m, 1H).

- 5 C. 6.7-Dimethoxynaphthalene-2-sulfonic acid {1-[3-(aminoiminomethyl)benzyl]-2-oxopyrrolidin-3-(S)-yl]amide trifluoroacetate.
 6,7-Dimethoxynaphthalene-2-sulfonic acid [1-(3-cyanobenzyl)-2-oxopyrrolidin-3-(S)-yl]amide is converted to the title compound as described in EXAMPLE 24, Part C. The imidate intermediate is formed over a period of 18 hours at room temperature. The amidine formation occurred over a period of 18 hours at room temperature. The crude product is purified by RP-HPLC eluting in a gradient of 10% CH₃CN/H₂O (0.1% TFA) to 60% CH₃CN/H₂O (0.1% TFA) and the appropriate product fractions are lyophilized to provide the title compound as a white solid.
- ¹H NMR (DMSO-d₆, 300 MHz) δ 9.29 (bs, 2H), 9.12 (bs, 2H), 8.28 (d, 1H), 8.09 (d, 1H), 7.90 (d, 1H), 7.67 (m, 2H), 7.52 (m, 4H), 7.40 (s, 1H), 4.40 (AB, 2H), 4.10 (m, 1H), 3.90 (s, 3H), 3.91 (s, 3H), 3.05 (m, 2H), 1.92 (m, 1H), 1.53 (m, 1H). ISP MS, [M+H]*=483. Elemental analysis calculated with 1.75 mole of H₂O: C=49.72%, H=4.89%, N=8.92%; found C=49.72%, H=4.41%, N=8.68%.

EXAMPLE 31

Naphtho(2.3-d)-(1.3)dioxole-6-sulfonic acid (1-[3-(aminoiminomethyl)benzyl]2-oxopyrrolidin-3-(S)-yl)amide trifluoroacetate.

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A: Naphtho(2.3-d)-(1.3)dioxole-6-sulfonyl chloride.

To a solution of 6,7-dihydroxynaphthalene-2-sulfonic acid, sodium salt (5 g, 18.4 mmol) in 40 mL of DMF is added cesium fluoride (14 g, 92.1 mmol) at room temperature. Dibromomethane (2.29 mL, 20.3 mmol) is added and the resulting mixture is heated at 120°C for 3 hours, and then allowed to cool to room temperature. A precipitate is formed after stirring overnight. A mixture of ice and water is added and the resulting mixture is diluted with acetone (100 mL). The crude mixture is concentrated in vacuo and the azeotrope with acetone is repeated twice to remove all the DMF. The crude residue is stirre in acetone to form a slurry and the solid is filtered and dried. The crude solic dissolved in 40 mL of 1 N NaOH solution and 95% EtOH (~100 mL) is added until a precipitate is formed and the solid is filtered and dried to give 1.49 g of the crude naphtho(2,3-d)-(1,3)dioxole-6-sulfonic acid, sodium salt. The crude

sulfonic acid, sodium salt (1.49 g, 5.27 mmol) is chlorinated in the presence of excess phosphorous oxychloride and phosphorous pentachloride as described in EXAMPLE 24, Part A to give the crude title compound. This product is of sufficient purity to be used in subsequent reactions.

¹H NMR (CDCl₃, 300 MHz) δ 8.37 (s, 1H), 7.82 (m, 2H), 7.26 (s, 1H), 7.19 (s, 5 1H), 6.16 (s, 2H). ¿Szflysmedűvútemonintsoúme;

4...7-Dimethoxynauhmatena-P. guifgnig oxopyrrolidin-3-(S)-vilamide. 24, Part C. The incidere intermediate

The title compound is prepared from 3-(3-(S)-amino-2-oxopyrrolidin-1-¹⁶10 ylmethyl)benzonitrile hydrochloride as in EXAMPLE 24, Part B using naphtho(2,3-d)-(1,3)dioxole-6-sulfonyl chloride in place of 6methoxynaphthalene-2-sulfonyl chloride. The crude product is triturated from and a configuration of the title compound as a beige solid. billog additive solid

 1 H NMR (CDCl₃, 300 MHz) δ 8.30 (s, 1H), 8.14 (d, 1H), 7.89 (d, 1H), 7.72 (m, 1H), 7.62 (m, 2H), 7.52 (m, 3H), 7.45 (s, 1H), 6.20 (s, 2H), 4.40 (AB, 2H), 4.15 (m, 1H), 3.07 (m, 2H), 1.98 (m, 1H), 1.57 (m, 1H) 200 6 111 m of 1

DP MS, [Mail]re445. Flamontal enalysis oplouts C. Naphtho(2,3-d)-(1,3)dioxole-6-sulfonic acid (1-[3-

- (aminoiminomethyl)benzyli-2-oxopyrrolidin-3-(S)-yl}amide trifluoroacetate: Naphtho(2,3-d)-(1,3)dioxole-6-sulfonic acid [1-(3-cyanobenzyl),2-x2 oxopyrrolidin-3-(S)-yl]amide is converted to the title compound as described in EXAMPLE 24, Part C. The imidate intermediate is formed over a period of 18 hours at room temperature. The amidine formation occurs over a period of 18 hours at room temperature. The crude product is purified by RP-HPLC eluting 25
 - in a gradient of 10% CH₃CN/H₂O (0.1% TFA) to 60% CH₃CN/H₂O (0.1% TFA) and the appropriate product fractions are lyophilized to provide the title Compound as a white solid.
- H NMR (DMSO-d_e, 300 MHz) δ 9.30 (bs, 2H), 9.10 (bs, 2H), 8.30 (s, 1H), 8.15 30 (d, 1H), 7.90 (d, 1H), 7.70 (m, 2H), 7.58 (m, 4H), 7.45 (s, 1H), 6.20 (s, 2H), 4.41 (AB, 2H), 4:12 (m, 1H), 3:10 (m, 2H), 1.99 (m, 1H), 1.56 (m, 1H)... ISP MS, [M+H]+=467. Elemental analysis calculated with 1.8 mole of H₂O: C=49.02%, H=4.37%, N=9.15%; found C=49.04%, H=3.98%, N=8.85%.
- acetone to a mile among a little solid is littered and to a your a mile acetone to 7-Benzyloxynaphthalene-2-sulfonic acid (1-[3-(amlnoiminomethyl)benzyl]-2oxopyrrolidin-3-(S)-vIlamide trifluoroacetate.

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EKAMPLE D3

morph and alter than tended a training of the fall of

A. 7-Benzyloxynaphthalene-2-sulfonyl chloride.

A 60% dispersion of sodium hydride (0.37 g. 9.22 mmol) in mineral oil is washed with hexanes twice and suspended in 40 mL of DMF. To this mixture is added slowly via an addition funnel 7-hydroxynaphthalene-2-sulfonic acid, sodium salt (1.25 g, 5.08 immol) in 25 mL of DMF at room temperature. The reaction mixture is stirred for 2 hours during which time mild bubbling is observed (H2 evolution). The mixture is treated with benzyl bromide (1.5 mL. 12.6 mmol) and stirred for 18 hours at room temperature. Ice is added to 10 decompose the excess NaH and the resultant mixture is concentrated in vacuo. The residue is suspended in acetone and concentrated in vacuo two times and then is dried under high vacuum. The solid is suspended in acetone, filtered and dried to yield the crude 7-benzyloxynaphthalene-2-sulfonic acid, sodium salt as a beige solid. A mixture of the sulfonic acid, sodium salt (2.47 g) in 8 mL 15 of thionyl chloride is heated at 80°C for 4 hours. A drop of DMF is added with vigorous bubbling resulting and the mixture is heated for an additional 30 minutes. The mixture is allowed to cool to room temperature and concentrated in yacuo The residue is diluted in EtOAc and washed successively with water (2x), saturated NaHCO₃ solution and saturated NaCl. The organic layer is 20 dried over anhydrous MgSO, filtered and concentrated to yield the title compound as a beige solid (1.26 g) 3.78 mmol). The crude product is of Resufficient purity to be used in subsequent reactions. 19.3 (HA 1) ¹H NMR (CDCl₃, 300 MHz) δ 8.46 (s, 1H), 7.97 (d, 1H), 7.83 (m, 2H), 7.45 (m, 6H), 7.33 (d, 1H), 5.28 (s, 2H).

25

s. [B--7-Benzyloxynaphthalene-2-sulfonic acid [1-(3-cyanobenzyl)-2-oxopyrrolidin-3-(S)-yl]amidestepsonoulilit ebimsity (S)-8-ninghiydaxi

2.sulfonyl chloride: The crude product is purified by column chromatography in a gradient of 10% Et@Ac/CH2Cl2 to 20% Et@Ac/CH2Cl2 to afford the title compound as a white solid and a bubong ebuno of 10% enumerations.

35,60,1H), 7.40 (m, 9H), 7.30 (d; 1H), 5.72 (s, 1H), 5.16 (d, 1H), 7.77 (m, 2H), 7.52 (m, 35,60,1H), 7.40 (m, 9H), 7.30 (d; 1H), 5.72 (s, 1H), 5.16 (s, 2H), 4.40 (s, 2H), 3.80 (m, 1H), 3.15 (m, 2H), 2.51 (m, 1H), 2.02 (m, 1H).

as a white solid.

77

C. 7-Benzyloxynaphthalene-2-sulfonic acid {1-[3-(aminoiminomethyl)benzyl]-2-oxopyrrolidin-3-(S)-yl}amide-trifluoroacetateidganyxolyzga3-7 A Hydrogen, sulfide gas is bubbled for 5 minutes through a solution of 7e wxim pin, benzyloxynaphthalene-2-sulfonic acid [1-(3-cyanobenzyl)-2-oxopŷrrolldin-3-5 onc (S)-yllamide (0.32 g., 0.63 mmol) in 10 mb of a 10:1 mixture of the si pyridine/triethylamine, After stirring the pale green solution for a period of 18 hours, the reaction mixture is concentrated in vacuo! The residue is diluted In acetone and concentrated to give the crude thioamide. To a solution of thioamide in 20 mL of acetone is added methyl iodide (2 mL; 32 mmol). The 01 10 Vac: resulting mixture is heated at reflux for 2 hours, allowed to cool to room temperature and concentrated in vacuo to provide the crude thiolmidate times and hydroiodide. To a solution of thioimidate hydroiodide in 20 mL of MeOH is added ammonium acetate (0.24 g. 3.17 mmol). The resulting mixture is heated at reflux for 3 hours, allowed to cool to room temperature and stirred overnight. 9) in e mi. 15 The resulting mixture is concentrated in vacuo to provide the crude amidine salt. The crude product is purified by RP-HPLC eluting in a gradient of 10% CH₂CN/H₂O (0.1% TFA) to 60% CH₃CN/H₂O (0.1% TFA) and the appropriate product fractions are lyophilized to provide the title compound (0:05 g; 0.08 (2x), saturated NaHCO, solution and saturated lyac etides as (lomm 20 19 H NMR (DMSO-d_{s.} 300 MHz) δ 9.30 (bs, 2H), 9.03 (bs, 2H), 8.35 (s. 1H), 8.21 (d, 1H), 8.01 (d, 1H), 7.95 (d, 1H), 7.71 (dd, 1H); 7.65 (m, 2H), 7.51 (m, 5H), 7.40 (m, 4H), 5.24 (s, 2H), 4.41 (AB, 2H), 4.18 (m, 1H), 3.08 (m, 2H), 1.98 (m, THE (CDC), 300 MHz) 8 8.625=[M+M] . 2M (SPI) (MI) . (CDC), 100 OB ... 6H), 7.33 (d, 1H), 5.28 (s, 2H). 25 **EXAMPLE 33** 25 7-Hydroxynaphthalene-2-sulfonic acid {1-[3-(aminoiminomethyl)benzyll-2oxopyrrolidin-3-(S)-yl)amide trifluoroacetate.ima(ly-(3)-3-nibilonyooxo The title compound is prepared from 3-(3-(S)-amino-2-exceyriched 7-Benzyloxynaphthalene-2-sulfonic acid [1-(3-cyanobenzyl)-2-oxopyrrolidin-3-(S)-yllamide is converted to the title compound as described in EXAMPLE 24, 30 Part C. The imidate intermediate is formed over a period of 18 hours at room temperature. The amidine formation occurred overla period of 42 hours at room temperature. The crude product is purified by RP-HPLC eluting in a gradient of 10% CH₃CN/H₂O (0.1% TFA) to 60% CH₃CN/H₂O (0.1% TFA) and the appropriate product fractions are lyophilized to provide the title compound

1H), 3.15 (i.i. 2H), 2.01 (m. 1H), 2.02 (m. 1H).

¹H NMR (DMSO-d₆, 300 MHz) δ 9.30 (bs, 2H), 9.08 (bs, 2H), 8.26 (s, 1H), 8.19 (d, 1H), 7.95 (d, 1H), 7.89 (d, 1H), 7.65 (m, 2H), 7.54 (m, 3H), 7.30 (d, 1H), 7.25 (dd, 1H), 4.44 (AB, 2H), 4.15 (m, 1H), 3.10 (m, 2H), 2.00 (m, 1H), 1.59 (m, 1H). FAB MS, [M+H] $^+$ = 439. Elemental analysis calculated with 2.6 mole of H₂O: C=48.13%, H=4.74%, N=9.35%; found C=48.14%, H=4.08%, N=9.32%.

EXAMPLE 34

6-Hydroxynaphthalene-2-sulfonic acid (1-[3-(aminoiminomethyl)benzyl]-2-oxopyrrolidin-3-(S)-yl)amide trifluoroacetate.

10

A. 6-Benzyloxynaphthalene-2-sulfonyl chloride.

The title compound is prepared as described in EXAMPLE 32, Part A using 6-hydroxynaphthalene-2-sulfonic acid, sodium salt in place of 7-hydroxynaphthalene-2-sulfonic acid, sodium salt. The crude

- 15 6-benzyloxynaphthalene-2-sulfonic acid, sodium salt obtained is likewise chlorinated with excess thionyl chloride and 3 drops of DMF. The crude product is triturated from 50% EtOAc/hexanes to give the title compound which is of sufficient purity to be used in subsequent reactions.

 14 NMR (CDCI₃, 300 MHz) δ 8.50 (d, 1H), 7.91 (m, 3H), 7.46 (m, 2H), 7.40 (m,
- 20 4H), 7.30 (d, 1H), 5.22 (s, 2H).

B. 6-Benzyloxynaphthalene-2-sulfonic acid [1-(3-cyanobenzyl)-2-) is oxopyrrolidin-3-(S)-yllamide. (F. L.) 38.5 is (SEM 0.00 , 60.00) is visited.

The title compound is prepared from 3-(3-(S)-amino-2-oxopyrrolidin-1-ylmethyl)benzonitrile hydrochloride as in EXAMPLE 24, Part B using 6-benzyloxynaphthalene-2-sulfonyl chloride in place of 6-methoxynaphthalene-2-sulfonyl chloride. The crude product is purified by column chromatography in a gradient of 10% EtOAc/CH₂Cl₂ to 25% EtOAc/CH₂Cl₂ to afford the title compound as a white solid

30 H NMR (CDCl₃, 300 MHz) δ 8.39 (s, 1H), 7.88 (d, 1H), 7.84 (m, 2H), 7.58 (m, 1H), 7.42 (m, 8H), 7.35 (dd, 1H), 7.25 (d, 1H), 5.52 (s, 1H), 5.21 (s, 2H), 4.43 (s, 2H), 3.75 (m, 1H), 3.20 (m, 2H), 2.60 (m, 1H), 2.08 (m, 1H).

C. 6-Hydroxynaphthalene-2-sulfonic acid-(1-[3-(aminoiminomethyl)benzyl]-2-oxopyrrolidin-3-(S)-yl]amide trifluoroacetate, susaqorqqs od bas (A-Y) 6-Benzyloxynaphthalene-2-sulfonic acid [1-(3-cyanobenzyl)-2-oxopyrrolidin-3-(S)-yl]amide is converted to the title compound as described in EXAMPLE 24,

Part C. The imidate intermediate is formed over a period of 18 hours at room temperature. The amidine formation occurred over a period of 18 hours at room temperature. The crude product is purified by RP-HPLC eluting in a gradient of 10% CH₂CN/H₂O (0.1% TFA) to 60% CH₂CN/H₂O (0.1% TFA) and 5 the appropriate product fractions are lyophilized to provide the title compound "Assarwhite solid."

H NMR (DMSO-d_e, 300 MHz) δ 9.33 (bs, 2H), 9.29 (bs, 2H), 8.33 (d, 1H), 8.11 (d, 1H), 7.96 (d, 1H), 7.85 (d, 1H), 7.74 (dd, 1H), 7.69 (m, 1H), 7.54 (m, 3H), 7.20 (m, 2H), 4.41 (AB, 2H), 4.12 (m, 1H), 3.07 (m, 2H), 1.96 (m, 1H), 1.57 (m, 1H). FAB MS, [M+H]*=439. Elemental analysis calculated with 2.2 mole of H₂O: C=48.64%, H=4.67%, N=9.45%; found C=48.63%, H=4.14%, N=9.52%.

Philad (EXAMPLE 35 MAX3 in bedinoseb as bensquage as bauoqmoe elit off 5-Chloro-3-methylbenzo (blithophene 2-sulfonic acid (1-13- (amino imino methyl) benzo (bloop chorus - and leading any xon trill uproacetate.

ebiAn 5-Chloro-3-methylbenzolblithiophene-2-sulfonic acid [1-(3-cyanobenzyl)-2-

The title compound is prepared from 3-(3-(S)-amino-2-oxopyrrolidin-1-

- ylmethyl)benzonitrile hydrochloride as in EXAMPLE 24, Part B using 5-chloro-3-methylbenzo[b]thiophene-2-sulfonyl chloride in place of 6methoxynaphthalene-2-sulfonyl chloride. The crude product is triturated from EtOAc to afford the title compound as a white solid.

 ¹H NMR (CDCl₃, 300 MHz) δ 7.82 (d, 1H), 7.78 (d, 1H), 7.60 (m, 1H), 7.45 (m, 4H), 5.59 (bs. 1H), 4.50 (s. 2H), 3.91 (m, 1H), 3.25 (m, 2H), 2.75 (s. 3H), 2.65
 - 25 -4H), 5.59 (bs, 1H), 4.50 (s, 2H), 3.91 (m, 1H), 3.25 (m, 2H), 2.75 (s, 3H), 2.65 (m, 1H), 2.14 (m, 1H) = 1.05 (m, 1H), 2.14 (m, 1H) = 1.05 (m, 1H) = 1.0
- (aminoiminomethyl)benzyll-2-oxopyrrolidin-3-(S)-yl\amide trifluoroacetate.
- 5-Chloro-3-methylbenzo[b]thiophene-2-sulfonic acid [1-(3-cyanobenzyl)-2-coxopyrrolidin-3-(S)-yl]amide is converted to the title compound as described in EXAMPLE 24; Part C. The imidate intermediate is formed over a period of 20 hours at room temperature. The amidine formation occurred over a period of 22 hours at room temperature. The crude product is purified by RP-HPLC
- 35 Se eluting in a gradient of 10% CH₃CN/H₂O (0.1% TFA) to 60% CH₃CN/H₂O (0.1% TFA) and the appropriate product fractions are lyophilized to provide the title appropriate a white solid. The significant enterty contains the title to the compound as a white solid. The significant enterty contains the containing th

¹H NMR (DMSO-d₆, 300 MHz) δ 9.32 (bs, 2H), 9.21 (bs, 2H), 8.76 (d, 1H), 8.09 (d, 1H), 8.04 (d, 1H), 7.68 (m, 1H), 7.53 (m, 4H), 4.41 (AB, 2H), 4.20 (m, 1H), 3.11 (m, 2H), 2.63 (s, 3H), 2.09 (m, 1H), 1.67 (m, 1H). FAB MS, [M+H] ⁺=477. Elemental analysis calculated with 1.7 mole of H₂O: C=44.37%, H=4.13%, N=9.00%; found C=44.37%, H=4.03%, N=8.66%.

EXAMPLE 36

5-Chloro-3-methylbenzo[b]thiophene-2-sulfonic acid {1-[3-(aminoiminomethyl)benzyl]-2-oxopyrrolidin-3-(S)-yl}methyl amide trifluoroacetate.

Lity 31.6 mil of) and 4-dimetriclamic opyridine (0.36

A. 5-Chloro-3-methylbenzo[b]thiophene-2-sulfonic acid [1-(3-cyanobenzyl)-2-oxopyrrolidin-3-(S)-vilmethyl amide.

The title compound is prepared as described in EXAMPLE 25, Part A using 5-chloro-3-methylbenzo[b]thiophene-2-sulfonic acid [1-(3-cyanobenzyl)-2-oxopyrrolidin-3-(S)-yl]amide as the starting material. The crude product is purified by column chromatography in a gradient of 2% EtOAc/CH₂Cl₂ to 10% EtOAc/CH₂Cl₂ to afford the title compound as a white solid.

1H NMR (CDCl₃, 300 MHz) δ 7.81 (s, 1H), 7.76 (d, 1H), 7.60 (m, 1H), 7.45 (m,

20 4H), 4.92 (m, 1H), 4.43 (AB, 2H), 3.23 (m, 2H), 2.90 (s, 3H), 2.72 (s, 3H), 2.41 (m, 1H), 2.09 (m, 1H).

B. 5-Chloro-3-methylbenzo[b]thiophene-2-sulfonic acid {1-[3-lossing aminoiminomethyl]benzyl]-2-oxopyrrolidin-3-(S)-yl}methyl amide

trifluoroacetate.

5-Chloro-3-methylbenzo[b]thiophene-2-sulfonic acid [1-(3-cyanobenzyl)-2-oxopyrrolidin-3-(S)-yllmethyl amide is converted to the title compound as described in EXAMPLE 24, Part C. The imidate intermediate is formed over a period of 24 hours at room temperature. The amidine formation occurred over 30 a period of 3 days at room temperature. The crude product is purified by RP-HPLC eluting in a gradient of 10% CH₃CN/H₂O (0.1% TFA) and the appropriate product fractions are lyophilized to provide the title compound as a white solid.

HNMR (DMSO-d₆, 300 MHz) 8 9.31 (bs, 2H), 9.19 (bs, 2H), 8.11 (d. 1H), 8.08

HNMR (DMSO-d_e, 300 MHz) 8 9.31 (bs, 2H), 9.19 (bs, 2H), 8.11 (d_e 1H), 8.08 (d, 1H), 7.68 (m, 1H), 7.56 (m, 4H), 4.94 (m, 1H), 4.42 (AB, 2H), 3.19 (m, 2H), 2.78 (s, 3H), 2.66 (s, 3H), 2.10 (m, 1H), 1.97 (m, 1H). FAB MS, [M+H]*=491.

Elemental analysis calculated with 0.9 mole of H₂O: C=46,43%, H=4.18%, N=9.02%; found C=46.42%, H=4.06%, N=8.90%, (H) 50.6 (H)

2 11 (m, 2' 5, 2 63 , 1 3H), 2.09 (m, 1H), 1.67 (m, 1H) FAE IAS [M]

Temental analysis relocated with 1.7 mole of H.O. (1=44.376, 14=

oxopyrrolidin-3-(S)-yl)amide trifluoroacetate.

EXAMILE 36 A. 2-Methoxy-7-trifluoromethanesulfonylnaphthalene. n. c. o:o/riQ-2 To a solution of 7-methoxy-2-naphthol (5 g, 28.7 mmol) in 150 mL CH₂Cl₂ at 0°C is added triethylamine (5.95 g, 58.8 mmol), trifluoromethanesulfonic 10 anhydride (10.1 g, 35.6 mmol) and 4-dimethylaminopyridine (0.36 g, 2.94 mmol). The brown solution is stirred for 1 hour at 0°C, then concentrated in washed with 1 N aqueous HCI, water, 10% Na₂CO₃ solution and saturated 15 ANaCl solution. The organic layer is dried over MgSO4 filtered and concentrated to provide crude material which is purified by column o chromatography in a gradient of 2% EtOAc/hexanes to 10% EtOAc/hexanes to afford the title compound (8.44 g, 27.5 mmol) as an oil of HO/cADE

¹H NMR (CDCI₃, 300 MHz) 8 7.90 (d, 1H), 7.78 (d, 1H), 7.65 (d, 1H), 7.22 (m, 413), 4 90 (11 111) 4 43 (A3, 7H), 3.43 (B, 2H), 2.30 (s, 3H), 2 72 (s, 3H), 1.45 (m) 1110 4 43 (A3, 7H), 3.43 (m, 2H), 2.30 (s, 3H), 2 72 (s, 3H), 1.45 (m)

(3), 11), 2.0° (5), 41).

B. 2-Methoxy-7-methylnaphthalene.

2-Methoxy-7-trifluoromethanesulfonylnaphthalene (10 g, 32.6 mmol) is dissolved in 300 mL of DMF and treated with lithium chloride (7,20 g, 170 mmol) and tetramethyltin (12.4 g, 69.3 mmol). Bis-

(triphenylphosphine)palladium(II) chloride (1.44 g, 2 mmol) is added and the resulting heterogeneous mixture is heated at 80°C for 18 hours. The reaction mixture is cooled to room temperature, filtered through a Celite pad and washed with EtOAc. The filtrate is washed with water and the layers separated.

The aqueous layer is extracted twice with EtOAc and the combined organic layers are washed with water and saturated NaCl solution. The organic layer is dried over MgSO4, filtered and concentrated to give crude material which is ath blee purified by column chromatography in a gradient of 2% EtOAc/hexanes to 5% EtOAc/hexanes to yield the title compound (5.34 g, 31 mmol) as a solid.

35 1H NMR (CDCl₃, 300 MHz) δ 7.69 (m, 2H), 7.52 (s, 1H), 7.19 (d, 1H), 7.10 (m, 2H), 3.93 (s, 3H), 2.50 (s, 3H). 278 (8 OH) 28- II. 3H), 2 H , C, III, CO (C, TH, FEG MS, IMH), ISS

C. 7-Methyl-2-naphthol.

A suspension of 2-methoxy-7-methylnaphthalene (5.30 g, 30.8 mmol) in 90 mL of 48% aqueous HBr is heated at reflux for a period of 2 hours. The resulting mixture is allowed to cool to room temperature, diluted with water and partially 5 neutralized with saturated NaHCO3 solution. The aqueous mixture is extracted with EtOAc twice and the combined organic layers are washed with water, saturated NaHCO₃ solution and saturated NaCl solution. The organic phase is and dried over MgSO₄, filtered and concentrated to provide crude material which is purified by column chromatography in a gradient of 5% EtOAc/hexanes to 20% 10c | EtOAc/hexanes to afford the title compound (3.05 g, 19.3 mmol) as a solid. ¹H NMR (CDCl_s, 300 MHz) δ 7.69 (m, 2H), 7.47 (s, 1H), 7.18 (m, 1H), 7.03 (m, 2H), 5.01 (m) 1H), 2.50 (s; 3H), care a restriction

D. 7-Methyl-2-trifluoromethanesulfonylnaphthalene.

15 7-Methyl-2-naphthol (3.05 g, 19.3 mmol) is converted to the title compound as described in EXAMPLE 37, Part A. The crude product is purified by column chromatography in a gradient of 2% EtOAc/hexanes to 10% EtOAc/hexanes to give the title compound (4.74 g, 16.3 mmol) as an oil. ¹H NMR (CDCl₃, 300 MHz) δ 7.89 (d, 1H), 7.80 (d, 1H), 7.69 (m, 2H), 7.40 (m,

the second copy and the social of 10 , Fighappy by the constitution of

1H), 7.30 (m, 1H), 2.59 (s, 3H). 20

E. 7-Methyl-2-trimethylstannylnaphthalene.

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7-Methyl-2-trifluoromethanesulfonylnaphthalene (1.50 g, 5.17 mmol) is dissolved in 30 mL of p-dioxane and treated with lithium chloride (0.66 g, 15.5 mmol) and hexamethylditin (1.86 g, 5.68 mmol). Bis-

- ((triphenylphosphine)palladium(II) chloride (0.30 g, 0.26 mmol) is added and the resulting heterogeneous mixture is heated at reflux for 1 hour. The reaction mixture is cooled to room temperature, diluted with 10% NH₄OH solution and CH, Cl, and stirred for 45 minutes. The layers are separated and the aqueous
- layer is extracted twice with $\widetilde{CH_2Cl_2}$. The combined organic layers are washed with saturated NaCl solution. The organic layer is dried over MgSO, filtered and concentrated to give crude material which is purified by column chromatography in a gradient of 2% EtOAc/hexanes to 5% EtOAc/hexanes to 15 yield the title compound (0.60 g, 1.97 mmol) as an oil.
- 35 s 1H NMR (CDCIs, 300 MHz) 87.90 (s, 1H), 7.75 (d, 1H), 7.70 (d, 1H), 7.60 (s, 1H), 7.51 (d, 1H), 7.30 (d, 1H), 2.54 (s, 3H), 0.34 (m, 9H).

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E. 7-Methylnaphthalene-2-sulfonyl chloride.ledidap.is2-sideM-X. Q To a solution of 7-methyl-2-trimethylstannylnaphthalene (0:60 g, 1.97 mmol) in 13 mL of THF at -78°C is added n-butyllithium (1940 mL of at 1.6 M solution in hexanes, 2.24 mmol), The reaction mixture is stirred for 5 min at 78°C then warmed to 0°C over a 30 min period: The mixture is cooled to 78°C again and the solution is transferred via cannula to a flask containing 10 mL of condensed 31 73810 SO2 (9) in 20 mL of THE at 78°C is The solution is stirred at 178°C for 10 of the least on the state of th mixture is concentrated in vacuo, triturated with Et2O and filtered. The solid is suspended in 8 mL of hexanes, cooled to 0°C and treated with sulfuryl chloride (1.70 mL of a 1M solution-in CH2Cl201.70 mmol). (The resulting solution is stirred for 15 minutes, and then concentrated. The crude residue is builfied by column chromatography in a gradient of 10% EtOAc/hexanes to 20% EtOAc/hexanes to afford the title compound (0.23 g, 0.96 mmol) as a solid. ¹H NMR (CDCI₃, 300 MHz) δ 8.51 (s; 1H), 8.01 (d, 1H), 7.92 dd, 1H), 7.89 (d, 1H), 7.80 (s. 1H), 7.58 (d. 1H), 2:58 (s. 3H), 78 R 14.4/XH ni bedhoseb presenting apply in a gradient of 19% EtOAc/hexanes to 10% EtOAc/tie order to G. 7-Methylnaphthalene-2-sulfonic acid [1-(3-cyanobenzyl)-2-oxopyrrolidin-3--1 On (S)-yllamide, 7 (Hr 15) 7 7 7 (Hr 16) 7 7 10 (Hr 16) 7 89 7 3 (EHM 000 1000) HMV-FI The title compound is prepared from 3-(3-(S)-amino-2-oxopyrrolidin-1ylmethyl)benzonitrile hydrochloride as in EXAMPLE 24, Part B using 7methylnaphthalene-2-sulfonyl,chloride in place of 6-methoxynaphthalene-2sulfonyl chloride. The crude product is triturated from 50% EtOAc/ hexanes to give the title compound as a white solid as other to the off ni peviousib ¹H NMR (CDCl₃, 300 MHz) δ 8.41 (s, 1H), 7.96 (s, 1H), 7.81 (m, 2H), 7.76 (s, 1 1H), 7.58 (m, 1H), 7.46 (m, 4H), 5.50 (bs, 1H), 4.47 (s, 2H), 3.79 (m, 1H), 3.20 (m, 2H), 2.59 (m, 1H), 2.55 (s, 3H), 2.10 (m, 1H) reposed a rituse, or 4 is 110.HM &0; this methic southenmet meet of bolice at studion. 7-Methylnaphthalene-2-sulfonic acid {1-[3-(aminoiminomethyl)benzyl]-2-

oxopyrrolidin-3-(S)-yl)amide trifluoroacetate. w epiwt befoutke at teys. 7-Methylnaphthalene-2-sulfonic acid [1-(3-cyanobenzyl)-2-oxopyrrolidin-3-(S)yl]amide is converted to the title compound as described in EXAMPLE 24, Part C. The imidate intermediate is formed over a period of 18 hours at room temperature. The amidine formation occurred over a period of 18 hours at room temperature. The crude product is purified by RP-HPLC eluting in a gradient of 10% CH₃CN/H₂O (0.1% TFA) to 60% CH₃CN/H₂O (0.1% TFA) and

)

the appropriate product fractions are lyophilized to provide the title compound as a white solid.

¹H NMR (DMSO-d₆, 300 MHz) δ 9.32 (bs, 2H), 9.28 (bs, 2H), 8.38 (s, 1H), 8.26 (d, 1H), 8.05 (d, 1H), 7.93 (d, 1H), 7.88 (s, 1H), 7.79 (dd, 1H), 7.65 (m, 1H), 7.52

- 5 (m, 4H), 4.41 (AB, 2H), 4.16 (m, 1H), 3.08 (m, 2H), 2.49 (s, 3H), 1.97 (m, 1H), 1.56 (m, 1H), FAB MS, [M+H]*=437. Elemental analysis calculated with 1.7 mole of H₂O: C=51.71%, H=4.92%, N=9.65%; found C=51.70%, H=4.66%, N=9.41%.
- 10. EXAMPLE 38. The substantial and the substa

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A. 2-Methoxy-7-trimethylstannylnaphthalene: - \ o but ex foo est

- The title compound is prepared as described in EXAMPLE 37, Part E using 2-methoxy-7-trifluoromethanesulfonylnaphthalene in place of 7-methyl-2-trifluoromethanesulfonylnaphthalene. The crude product is purified by column chromatography in a gradient of 2% EtOAc/hexanes to 5% EtOAc/hexanes to afford the title compound as an oil.
- 20 1H NMR (CDCl₃, 300 MHz) δ.7.89 (s, 1H), 7.70 (m, 2H), 7.43 (d, 1H), 7.35 (s, 1H), 7.12 (m, 1H), 3.91 (s, 3H), 0.39 (m, 9H):

2) 10 B. 2-Methoxy-7-ethylnaphthálene) 36.86 (seise 600 atomb) 1994 H

To a solution of 2-methoxy-7-trimethylstannylnaphthálene (1.61 g, 3.60 mmol)

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- in 24 mL of THF at -78°C is added n-butyllithium (2.80 mL of a 1.6 M solution in hexanes, 4.48 mmol) The reaction mixture is stirred for 5 min at -78°C then warmed to 0°C over a 30 min period. The mixture is cooled to -78°C again and bromoethane (1.46 gm13.4 mmol) is added: The solution is stirred at -78°C for 10 minutes, and then at ambient temperature for 4 hours. At this time, the
- reaction mixture is quenched with saturated NH₄Cl solution diluted with EtOAc and the layers are separated. The organic layer is washed with 1 N aqueous HCl, water, saturated NaHCO₃ solution and saturated NaCl solution. The corganic layer is dried over MgSO₄, filtered and concentrated to product which is purified by column chromatography in a gradient of 2%
- 35 EtOAc/hexanes to 5% EtOAc/hexanes to give a 3.5:1 mixture (0.56 g) 3.01 mmol) of the title compound as the major component and 2-methoxynaphthalene as the minor component.

7.3

27-1-1-100-1H NMR (CDCl₃, 300 MHz) δ 7.72 (m; 2H); 7.54 (s; 1H), 7.32 (s; 1H), 7.11 (d, 1H), 7.08 (s, 1H), 3.90 (s, 3H), 2.80 (q, 2H), 1.31 (t, 3H); a selicity a se H (3MA) (DMAO-LL, 300 MHz) 5 3.72 (bs. 2H), 7.23 (bs. 2H), 8.33 (c. 1H), 125 Service (d. 14), 7.9 (d. 14), 1 5 n) A mixture of 7-ethyl-2-naphthol and naphthol is prepared as described in EXAMPLE 37 Part C using the 3.5-1 mixture of 2-methoxy-7-ethylnaphthalene 3 sand 2-methoxynaphthalene in place of 2-methoxy-7-methylnaphthalene. The crude demethylated product is partially purified by column chromatography in a gradient of 5% EtOAc/hexanes to 20% EtOAc/hexanes. The 7-ethyl-2-naphthol mixture is converted to 7-ethyl-2-trifluoromethanesulfonylnaphthalene as 10 -S-I described in EXAMPLE 37 Part An The crude triflated material is partially purified by column chromatography in a gradient of 2% EtOAc/hexanes to 5% EtOAc/hexanes. The crude 7-ethyl-2-trifluoromethanesulfonylnaphthalene is then converted to 7-ethyl-2-trimethylstannylnaphthalene as described in -S p15 partially purified by column chromatography in a gradient of 2% EtOAc/hexanes to 5% EtOAc/hexanes. The 7-ethyl-2-trimethylstannylnaphthalene is converted to the title compound THE BENEFIX AS, described in EXAMPLE 37, Part Flusing 7-ethyl-24/1989-0018-0019 trimethylstannylnaphthalene in place of 7-methyl-2200 ethi enterviews 20 S trimethylstamylnaphthalene and Et O in place of THF. The crude mixture is purified by column chromatography in a gradient of 5% EtOAc/hexanes to 10% EtOAc/hexanes to afford the title compound as an oil. ¹H NMR (CDCl₃, 300 MHz) δ 8.54 (s;:1H);:8:01 (d;:1H),\7.90 (m;:1H), 7.87 (s. To a sciule of 1H), 7.81, (s. 1H), 7.61, (d. 1H), 2.88 (q. 2H), 1.35 (t. 3H); politics a of In 21 art of THE at -75°C is adred n-buryllimidm; (2.80 mt. of a 1.3 M ac. 45-n b na # : D. 7-Ethylnaphthalene-2-sulfonic acid 1-(3-cvanobenzyl)-2-ôxôpyrrolidin-3warmed to 0°C over a 50 min period. The mixture is conediminity a series of The title compound is prepared from 3-(3-(8)-amino-2-oxopyrrolidin-1-913 ylmethyl)benzonitrile hydrochloride as in EXAMPLE 24. Part Busing 7-30 Hethylnaphthalene-2-sulfonyl chloride in place of 6-methoxynaphthalene-2sulfonyl chloride. The crude product is triturated from 50% EtOAc/hexanes to HOL werer, saturated NaHOObilosietidwas as bnuogmooglit, edit, eyig it of 1H NMR₁(CDCl₃, 300 MHz) δ.8:41i(s, 4H);7.96 (d, 1H); 7.85 (m, 2H);7.75 (s. 361H), 7.55 (m, 2H), 7.45 (m, 3H), 5.42 (s, 1H), 4.46 (AB, 2H), 3.76 (m, 1H), 3.20 35 ე _s(m, 2H); 2.85 (g, 2H), 2.60 (m; 1H), 2.10 (m, 1H), 1.39 (t; 3H) ამ აბმ

ment, of the lifts considered as the major component and 2

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E. 7-Ethylnaphthalene-2-sulfonic acid (1-[3-(aminoiminomethyl)benzyl]-2-oxopyrrolidin-3-(S)-yl}amide trifluoroacetate.

7-Ethylnaphthalene-2-sulfonic acid [1-(3-cyanobenzyl)-2-oxopyrrolidin-3-(S)-yl]amide is converted to the title compound as described in EXAMPLE 24, Part C. The imidate intermediate is formed over a period of 18 hours at room temperature. The amidine formation occurred over a period of 3 days at room temperature. The crude product is purified by RP-HPLC eluting in a gradient of 10% CH₃CN/H₂O (0.1% TFA) to 60% CH₃CN/H₂O (0.1% TFA) and the appropriate product fractions are lyophilized to provide the title compound as a

white solid: (b, 300 MHz) δ 9.30 (bs, 2H), 9.20 (bs, 2H), 8.40 (s, 1H), 8.25 (d, 1H), 8.07 (d, 1H), 7.97 (d, 1H), 7.90 (s, 1H), 7.80 (dd, 1H), 7.68 (m, 1H), 7.55 (m, 4H), 4.43 (AB, 2H), 4.16 (m, 1H), 3.10 (m, 2H), 2.80 (q, 2H), 1.97 (m, 1H), 1.59 (m, 1H), 1.30 (t, 3H), FAB MS; [M+H]*=451. Elemental analysis

15. calculated with 1:6 mole of H₂O; C=52.67%, H=5.13%, N=9.45%; found C=52.65%, H=4.60%, N=9.17% neighbors are calculated with 1:6 mole of H₂O; C=52.65%, H=4.60%, N=9.17% neighbors are calculated as a constant of the constant of the

3 1 5 - Chloro-6-aminonaphthalene-2-sulfonic acid (1-[3-13-14]

20. (aminoiminomethyl)benzylj-2-oʻxopyrrölidin-3-(S)-yi)amide bistriffilioroacetate.

A. N-Cbz-5-Chloro-6-aminonaphthalene-2-sulfonic acid, sodium salt (3 g, 12.2

Oxopy with the 4-(5) making a material council and income the community and the comm

25 temperature. The mixture is stirred for 1 hour, and benzyl chloroformate (3.43 mL; 24 mmol) is then added. The resulting mixture is stirred over a period of 16 hours. The crude product is treated as in EXAMPLE 24, Part A to give 4.70 g of crude N-CBz-6-aminonaphthalene-2-sulfonic acid, sodium salt. A mixture of the sulfonic acid, sodium salt (2.3 g, 6.10 mmol) in 15 mL of thionyl chloride is

heated at 80°C for 5 hours. The mixture is allowed to cool to room temperature and concentrated in vacuo. The residue is diluted with EtOAc and washed successively with water (2x), saturated NaHCO₃ solution and saturated NaCl. The organic layer is dried over anhydrous MgSO₄ filtered and concentrated to give a solid. The crude product is triturated from 50% EtOAc/hexanes to afford

35 the title compound (0.50 g; 1.33 mmol) as a beige solid.

1H NMR (CDCI₃:300 MHz) δ 8.75 (d, 1H), 8.60 (d, 1H), 8.39 (d, 1H), 8.09 (dd, 1H), 8.00 (d, 1H), 7.68 (d, 1H), 7.46 (m, 5H), 5.30 (s, 2H).

E. 7-Envioachhaler a-2-sulionic acid (1-13-(or inclining nathythar cvi'-2 B. N-Cbz-5-Chloro-6-aminonaphthalene-2-sulfonic acid [1-(3-cvanobenzyl)-2-7-Ethylnaph/halene-2-sulfonic acid (1.abimafly-(3)-6-nibilonyqoxo 3-1 59 - The title compound is prepared from 3-(3-(S)-amino-2-oxopyrrolidin-1-5 ylmethyl)benzonitrile hydrochloride as in EXAMPLE 24 Part B using N-Cbz-5chloro-6-aminonaphthalene-2-sulfonyl chloride in place of 6-19 quite methoxynaphthalene-2-sulfonyl chloride withe crude product is purified by column, chromatography, using a gradient of 10% EtOAc/CH2Cl2 to 25% EtOAc/CH₂Cl₂ to give the title compound as a solid bond ensurage and high NMR (CDCL and MH=) see 40 / 1 = 10 ¹H NMR (CDCl₃, 300 MHz) δ 8.49 (d, 1H), 8.41 (s, 1H), 8.15 (d, 1H), 7.99 (d, 35 8 (Ht 1H), 7,80 (d, 1H), 7,60 ((sc1H)), 7,45 (m,9H); 6:30 (d,4H))/5:29 (s; 2H), 4.45 (s. 2H), 3.97 (m, 1H), 3.20 (m, 2H), 2.55 (m, HH), 2.06 (m, HH). 8 (Ht , b) (m, aH), 4.43 (AB, 2H), 4.16 (m, 1H), 3.10 (m, 2H), 2.80 (q, 2H), 1.87 (m, 1H) 5-Chloro-6-aminonaphthalene-2-sulfonic acid [1-[3-(Ht.,m) 62.1 15 (aminoiminomethyl)benzyl]-2-oxopyrrolidin-3-(S)-yl]amide bistrifluoroacetate. N-Cbz-5-Chloro-6-aminonaphthalene-2-sulfonic acid-[1-(3-cyanobenzyi)-2oxopyrrolidin-3-(S)-yl]amide is converted to the title compound as described in EXAMPLE 24, Part C. The imidate intermediate is formed over a period of 3 days at room temperature. The amidine formation occurred over a period of 18 hours at room temperature. The crude product is purified by RP-HPLC eluting 20 in a gradient of 10% CH₃CN/H₂O (0.1% TFA) to 60% CH₃CN/H₂O (0.1% TFA) and the appropriate product fractions are lyophilized to provide the title To a suspension of 6-aminor aprilies - bilos etilos as a brigography 1H NMH (DMSO-d_a, 300 MHz) δ 9.28 (bs, 2H), 9.10 (bs, 2H), 8.25 (d.11H), 8.09 (d, 1H), 7.95 (d, 1H), 7.81 (m, 2H), 7.65 (m, 1H), 7.50 (m, 3H), 7:20 (d, 1H), 4.40 (AB, 2H), 4.10 (m, 1H), 3.06 (m, 2H), 1.95 (m, 1H), 1.52 (m, 1H). FAB MS, Louis. The crude product is treated as in EXAMPLE 24, Part A to give าเมสัง N-CE. เรื่อยกักรอกสุดิที่โดยโอก**e-2-s**ulionic ฮอโต รอดีเม<u>m selt</u> the selfon cleck, sodium self (2.3 g, 6.10 mniol) in 15 mL or micros ch กับ โงกังก็ที่ To Jam & I ne (เอเกเก บา.อ. เมื่อ อาวาระ 7-Methylaminonaphthalene-2-sulfonic acid (1-[3-(aminoiminomethyl)bธารังไ]-2a 2 Holdo 7-T.U. 5104 scarda.s. modification to constant the property of the propert successively with viater (2x), saturated NaHCO, solution and saturated NaCI N-Cbz-7-Methylaminonaphthalene-2-sulfonyl-chloride: oinsground N-Cbz-7-Aminonaphthalene-2-sulfonic acid, sodium salt is prepared as 35 described in EXAMPLE 39, Part A using 7-aminonaphthalene-2-sulfonic acid, sodium salt (3 g, 12.2 mmol) in place of 6-aminonaphthalene-2-sulfonic acid.

sodium salt. A 60% dispersion of sodium hydride (0.21:g, 5.27 mmol) in

mineral oil is washed with hexanes twice, suspended in 20 mL of DMF and the resulting suspension is cooled to 0°C. To this mixture is added the crude N-Cbz-7-aminonaphthalene-2-sulfonic acid, sodium salt (1 g, 2.64 mmol) in 15 mL of DMF. The reaction mixture is stirred for 10 min at 0°C and then treated

- with methyl iodide (0.49 mL; 7.92 mmol). The resulting mixture is allowed to warm to room temperature with stirring overnight. The reaction mixture is worked up according to the similar procedure used in EXAMPLE 32, Part A to yield the crude N-Cbz-7-methylaminonaphthalene-2-sulfonic acid, sodium salt (0.88 g) as a beige solid. A mixture of the sulfonic acid, sodium salt (0.88 g,
- 2.23 mmol) is chlorinated as described in EXAMPLE 32, Part A. The crude product is purified by column chromatography in a gradient of 10% EtOAc/hexanes to 30% EtOAc/hexanes to afford the title compound (0.33 g, 0.97 mmol) as a being solid.

1H NMR (CDCI₃, 300 MHz) δ 8.55 (d, 1H), 7.98 (m, 3H), 7.84 (s, 1H), 7.75 (d,

15 1H), 7.38 (m, 5H), 5.25 (s, 2H), 3.50 (s, 3H). இயியம் நடிகள்கள் செய்யார்கள் செய்யார்கள் செய்யார்கள் செய்யார்கள்

e: B.e:N-Cbz-7-Methylaminonaphthalene-2-sulfonic acid [1-(3-cyanobenzyl)-2-oxopyrrolidin-3-(S)-yl]amide. diw below benefic exhibits which

The title compound is prepared from 3-(3-(S)-amino-2-oxopyrrolidin-1-

- 20 ylmethyl)benzonitrile hydrochloride as in EXAMPLE 24, Part B using N-Cbz-7-methylaminonaphthalene-2-sulfonyl chloride in place of 6-methoxynaphthalene-2-sulfonyl chloride. The crude product is purified by column chromatography using a gradient of 10% EtOAc/CH₂Cl₂ to 25% EtOAc/CH₂Cl₂ to give the title compound as a solid.
- 25 -{H·NMR (CDCl₃; 300 MHz) 8 8:41 (s, 1H), 7:97 (d, 1H), 7:87 (m, 2H), 7.80 (s, -9H), 7:60 (m, 2H), 7:45 (m, 9H), 7:38 (m, 5H), 5:53 (bs, 1H), 5:51 (s, 2H), 4:43 (b) (s, 2H), 3:79 (m, 1H), 3:45 (s, 3H), 3:20 (m, 2H), 2:60 (m, 1H), 2:10 (m, 1H).

or 30 tCNo7-Methýlaminonabhthálene-2-súlfonic ácid 11-13-mulos ya bentiug

- (aminoiminomethyl)benzyll-2-oxopyrrolidin-3-(S)-yl)amide bistrifluoroacetate.

 N-Cbz-7-Methylaminonaphthalene-2-sulfonic acid [1-(3-cyanobenzyl)-2-oxopyrrolidin-3-(S)-yl]amide is converted to the title compound as described in EXAMPLE 24, Part C. The imidate intermediate is formed over a period of 48 hours at room temperature. The amidine formation occurred over a period of 3
- a gradient of 10% CH₃CN/H₂O (0.1% TFA) to 60% CH₃CN/H₂O (0.1% TFA) and

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and the appropriate product fractions are lyophilized to provide the title compound
      resulting suppersion is cooled to 3.0. To this mixturally editing a resulting
     TH NMR (DMSO-de, 300 MHz), δ.9.28 (bs, 2H), 9.08 (bs, 2H), 8.11 (s) 1H). 8.08
    1.31,034 (d, 1.14), 7.80 (d, 1.14), 7.70 (d, 1.14), 7.68 (m, 1.14), 2.54 (m, 3H)(.7:45) (dd, 1H).
      of b.5, 17.08 (dd, 1H), 6.80 (d, 1H), 4.42 (AB, 2H), 4.10 (m, 1H), 3.05 (m, 2H), 2.77 (s.
              3i enu 3H), 1.93 (m, e1H), 1.51 (m, e1H), FAB MS [M+H] = 452 Felemental analysis
  calculated with 0.9 mole of H2O; C=46.64%; H=4:17%; N=10.07%; found
yield the crude w. Chz-7-methylan %61,01 = 1.00, N=1.01 = 1.00 or the scale scale of the scale o
         (0.98.5) ac a beign solid. A mixture of the suitonic acid, sodium salt (0.88.5) 01. 22.3 mmol) is chlorinated as described in EXAMPLE 32 mmol) is chlorinated as described in EXAMPLE 32 mmol).
                                                                                                                                                                                                                       01
                             2-Methyl-1.2.3.4-tetrahydroisoguinoline-7-sulfonic acid (1-[3-cuborq
          p (1.0) (aminoiminomethyl)benzyll-2-oxopyrrolidin-3-(S)-yl}amide bistrifluoroacetate.
                                                                                                                                    0.97 mmol) as a beige solid.
        b) at 7 A. 2-Trifluoromethylacetamide-1.2.3.4-tetrahydro-isoquiñoline-7-sulfonyl
                             chloride.
                                                                                               fri), 7.38 (m, 5H), 5.25 (s, 2H) 3.50 (s, 3H)
                            The title compound is prepared according to the procedure described in J.
                            Med. Chem., 23, 837 (1980) which is incorporated herein by reference. The
                            crude residue obtained is triturated with Et,O to yield product which is of
                            sufficient purity to be used in subsequent reactions rucomon add entit
                              H NMR (CDCI<sub>3</sub>, 300 MHz) δ.7.90 (m, 2H), 7.49 (m, 1H), 4.90 (s. 2H), 3.95 (m,
                           anethylaminonaphthalane-2-sulfonyl chloride in plates 3.10 (m, 2H). 3.10
              metho-greaphthale-re-2-suffortylichloride. The crude product is purified by
                                     2-Trifluoromethylacetamide-1.2.3.4-tetrahydro-isoguinoline-7-sulfonic acid
                           [1-(3-cyanobenzyl)-2-oxopyrrolidin-3-($)-yl]amide:p or 10,140/5AO:H
           25 The title compound is prepared from 3-(3-(S)-amino-2-exopyrrolidin-1-
                           ylmethyl)benzonitrile hydrochloride as in EXAMPLE 24, Part B using 2-
                           trifluoromethylacetamide-1,2,3,4-tetrahydro-isoquinoline-7-sulfonyl chloride in
                           place of 6-methoxynaphthalene-2-sulfonyl chloride. The crude product is
                           purified by column chromatography using a gradient of 10% EtOAc/CH,Cl, to
                          25% EtOAc/CH2Cl2 to give the title compound as a solid nonimonimal
                        H NMR (CDCI, 300 MHz) & 7.79 (m, 2H), 7.63 (m, 1H), 7.50 (m, 3H), 7.39 (m,
                           1H), 5.50 (bs, 1H), 4.90 (AB, 2H), 4.49 (AB, 2H), 3.91 (m, 2H), 3.79 (m, 1H),
        EXAMPLE 24, 16, (m), 2H), 3.05 (m, 2H), 2.69 (m, 1H), 2.10 (m) 1H) a AS 3 19MAX3
                          hours at noon temperature. The amidine formetion occurred over a occurred over
                         a grade to the training a child (Child and the child and the training a
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To a solution of 2-trifluoromethylacetamide-1,2,3,4-tetrahydro-isoquinoline-7-sulfonic acid [1-(3-cyanobenzyl)-2-oxopyrrolidin-3-(S)-yl]amide (0.50 g, 0.99 mmol) in 6 mL of EtOH is added a solution of sodium carbonate (0.56 g, 5.27 mmol) in 6 mL of H₂O. The solution is stirred at room temperature for 5 hours.

After this time, the solution is concentrated in vacuo, diluted with CH₂Cl₂ and washed with H₂O and saturated NaCl solution. The organic phase is dried over anhydrous MgSO₄, filtered and concentrated to yield the title compound (0.29 g, 0.71 mmol) as a beige solid.

10 + 1H), 4.50 (s, 2H), 4.10 (s, 2H), 3.75 (m, 1H), 3.20 (m, 4H), 2.90 (m, 2H), 2.60 (m, 2H), 2.10 (m, 1H), 2.10 (m, 1H), 3.20 (m, 2H), 3.75 (m, 4H), 3.20 (m, 4H), 3.20 (m, 2H), 3.60 (m, 2H), 3.60

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D.-2-Methyl-1:2.3.4-tetrahydro-isoquinoline-7-sulfönic acid (1-[3] (aminoiminomethyl)benzyl]-2-oxopyrrolidin-3-(S)-vi)amide bistriffuoroacetate.

- To a solution of 1,2,3,4-tetrahydro-Isoquinoline-7-sulfonic acid [1-(3-cyanobenzyl)-2-oxopyrrolidin-3-(S)-yl]amide (0.29 g, 0.71 mmol) in 10 mL of CH₂Cl₂ is added 0.27 mL of 37% aqueous formaldehyde. The solution is stirred at room temperature for 1 hour. After this time, sodium
- triacetoxyborohydride (0.05 g, 0.22 mmol) is added and the resulting mixture is stirred for 18 hours. The reaction mixture is diluted with CH₂Cl₂ and washed with saturated NaHCO₃ solution. The organic phase is dried over anhydrous MgSO₄, filtered and concentrated to give 2-methyl-1,2;3,4-tetrahydro-isoquinoline-7-sulfonic acid [1±(3-cyanobenzyl)-2-oxopyrrolidin-3-(S)-yl]amide (0.16 g, 0.71 mmol) as a solid. The crude methylated material is then
- converted to the title compound as described in EXAMPLE 24, Part C. The similate intermediate is formed over a period of 18 hours at room temperature.

 The amidine formation occurred upon heating at reflux for 2 hours. The crude product is purified by RP-HPLC eluting in a gradient of 10% CH₃CN/H₂O (0.1% TFA) to 60% CH₃CN/H₂O (0.1% TFA) and the appropriate product fractions are
- 30 lyophilized to provide the title compound as a white solid. 3 1 (bs. 2H), 8.26 (d, 1H), 7.75 (m, 3H), 7.57 (m, 3H), 7.49 (d, 1H), 4.60 (s, 1H), 4.45 (s, 2H), 4.40 (m, 1H), 4.15 (m, 1H)):3:40 (m, 2H), 3:15 (m, 4H), 2:95 (s, 3H), 2:10 (m, 1H), 1.62 (m, 1H).

 FAB:MS, [M+H] = 442. Elemental analysis calculated with 2.2 mole of H₂O:
- (35 mC=44.03%,tH=4.75%, N=9.87%; found C=44.03%; H=4.28%, N=9.96%.

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-พ-รถและ 1.2.3.4-Tetrahydroisogulnoline-7-sulfonic acid (1-43-to กาสมโดย ธ.บโ eg ந daminoiminomethyl)benzyll-2-oxopyrrolidin-3-(S)-yl)methyl amide minol) in 6 inL of EtOH is added a solution of sodiumebiroldoorbydib; a, 3,27 mimoly in 5 oil, of H₂O - itie solution is stirred at room temperature for 5 hours. 30,5 3 A. 1:2.3:4-Tetrahydroisoguinoline-7-sulfonic acid [1-(3-cvanobenzyi)-2washed with H2O and saturated abims high method with H2O. on a 2-Trifluoromethylacetamide-1,2,3,4-tetrahydroisoguinoline-7-sulfonic acid [1-(3-cyanobenzyl)-2-oxopyrrolidin-3-(S)-yl]methyl:amlde is prepared as described in EXAMPLE 25, Part A using 2-trifluoromethylacetamide 1,2,3,4-10 tetrahydro-isoquinoline-7-sulfonic acid [1-(3-cyanobenzyl)-2-oxopyrrolidin-3-(S)-yl]amide as the starting material. The crude material is purified by column chromatography in 25% EtOAc/CH2Cl2 to afford the methylated product as a solide: The title compound is prepared as described in EXAMPLE 41 Part C using 2-trifluoromethylacetamide-1,2,3,4-tetrahydro-isoquinoline-7-sulfonic acid [1-(3-cyanobenzyl)-2-oxopyrrolidin-3-(S)-yl]methyl amide as the starting material. The crude product is triturated from:50% EtOAc/CH2Cl; to afford the CH₂Cl₂ is added 0.27 mil of 37% signeous febilos as a bnuoqmon elitin is 1H NMR, (CDCI₃, 300, MHz), δ·7.71; (dd, 11H), 7.62 (m; 2H), 7.50 (m; 3H), 7.25 (s, ... 4 Harris, n1H), 14.90 (m, 1H), 4.47 (AB, 2H), 4.10 (s, 2H), 3.20 (m, 4H), 2.90 (m, 2H), 2.79 120 (s,3H), 2.36 (m, 1H), 2.05 (m, 1H) a reducer of it of certite with calurated Nat ICO, solution. The organic phase is aded over aphydrous B. 1.2:3.4-Tetrahydroisoguinoline-7-sulfonic acid (1-73-59 office) OSpM 20 mariy (aminoiminomethyl)benzyl]-2-oxopyrrolidin-3-(S)-vl]methyl amide post dihydrochloride, pelityliai en orude melitylaited. en orude melitylaited. 25 1,2,3,4-Tetrahydro-isoquinoline-7-sulfonic acid [1-(3-cyanobenzyl)-220 oxopyrrolidin-3-(S)-y[]methyl amide is converted to the title compound as described in EXAMPLE 24, Part Co. The imidate intermediate is formed over a period of 18 hours at room temperature. The amidine formation occurred upon heating at reflux for 1.5 hours. The crude product is purified by RF-HPLO eluting in a gradient of 10% CH3CN/H2O to 60% CH3CN/H2O and the appropriate product fractions are lyophilized to provide the title compound as a (a), 3H), 7.37 (m, 3H), 7.49 (d, 1H), 4.60 (s. 3H), 4.46 (s. 2H). bilos etime. H NMR (DMSO-d_s, 300 MHz) 8,9.69 (bs, 2H), 9.46 (bs, 2H), 9.20 (bs, 2H), 7.78 (s, 1H), 7.73 (m, 2H), 7.60 (m, 3H), 7.44 (d, 1H), 4.89 (m, 1H), 4.44 (AB, 2H), 4.32 (s, 2H), 3.32 (m, 2H), 3.18 (m, 2H), 3.09 (m, 2H), 2.64 (s, 3H), 2.03 (m, 1H). 35 1.80 (m, 1H). FAB MS, [M+H]+=442.

EXAMPLE 45

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7-Methoxynaphthalene-2-sulfonic acid {1-[3-(aminoiminomethyl)benzyl]-2-oxopyrrolidin-3-(S)-yl}-(4-nitrobenzyl)amide trifluoroacetate.

5 83 A. 7-Methoxynaphthalene-2-sulfonic acid [1-(3-cyanobenzyl)-2-oxopyrrolidin-3-(S)-yl]amide.

The title compound is prepared from 3-(3-(S)-amino-2-oxopyrrolidin-1-ylmethyl)benzonitrile hydrochloride as in EXAMPLE 24, Part B using 7-methoxynaphthalene-2-sulfonyl chloride in place of 6-methoxynaphthalene-2-sulfonyl chloride. The crude product is triturated from EtOAc to give the title compound as a white solid.

¹H NMR (CDCl₃; 300 MHz) δ 8.38 (d, 1H), 7.91 (d, 1H), 7.81 (d, 1H), 7.73 (dd, 3H), 7.59 (m; 1H), 7.42 (m, 3H), 7.30 (dd, 1H), 7.25 (m; 1H), 5.39 (d, 1H), 4.45 (AB; 2H), 3.92 (s, 3H), 3.75 (m, 1H), 3.20 (m, 2H), 2.60 (m, 1H), 2.10 (m, 1H).

15 on adhibition of the helpingprocess mix are is by transmitted to 15

B. 7-Methoxynaphthalene-2-sulfonic-acid-[1-(3-cyanobenzyl)-2-oxopyrrolidin-3-(S)-yl]-(4-nitrobenzyl)amide: a cent expend because it cold as w

The title compound is prepared as described in EXAMPLE 25, Part A using 7the transport of the title compound is prepared as described in EXAMPLE 25, Part A using 7the title compound is prepared as described in EXAMPLE 25, Part A using 7the title compound is prepared as described in EXAMPLE 25, Part A using 7the title compound is prepared as described in EXAMPLE 25, Part A using 7the title compound is prepared as described in EXAMPLE 25, Part A using 7-

- 20, yl]amide as the starting material and p-nitrobenzyl bromide in place of methyl iodide. The crude product is purified by column chromatography in 50% EtOAc/hexanes to afford the title compound as a solid. All Styles.
- (d, 1H), 7.84 (d, 2H), 7.81((d, 1H), 7.60 (m, 3H), 7.50 (s, 1H), 7.45 (d, 2H), 7.51 (m, 1H), 7.19 (d, 2H), 7.51 (m, 2H), 7.51 (
 - 25: (3H);(4:65:(AB, 2H)); 4.50 (m, 1H); 4.38 (AB) 2H), 3.97 (s, 3H), 3:17 (m, 2H), 2.41
 - C. 7-Methoxynaphthalene-2-sulfonic acid (1-[3-(aminoiminomethyl)benzyl]-2-oxopyrrolidin-3-(S)-yl}-(4-nitrobenzyl)amide trifluoroacetate.

Head 4.1%, N=8 56% found C=50.61% H=4 21.% Na.6.64%

- 30 7-Methoxynaphthalene-2-sulfonic acid [1-(3-cyanobenzyl) 2-oxopyrrolidin-3-(S)-yl]-(4-nitrobenzyl)amide is converted to the title compound as described in EXAMPLE 24, Part C. The imidate intermediate is formed over a period of 18 hours attroom temperature. The amidine formation occurred upon heating at reflux for 1 hour. The crude product is purified by RP-HPLC eluting in a
- 35 gradient, of: 10% CH3CN/H2O (0:1% TFA) to 60% CH3CN/H2O (0:1% TFA) and முத்திரு வரும் பிரியில் முற்றியில் முறியில் முற்றியில் முற்றியில் முற்றியில் முற்றியில் முற்றியில் முறியில் முற்றியில் முற்றியில் முற்றியில் முற்றியில் முறியில் முறியில்

¹H NMR (DMSO-d₈, 300 MHz) δ 9.30 (bs, 2H), 9.25 (bs, 2H), 8.38 (s, 1H), 8.13 (d, 2H), 8.04 (d, 1H), 7.96 (d, 1H), 7.80 (dd, 1H), 7.70 (m, 3H), 7.55 (m, 4H), 7.34 (dd, 1H), 4.94 (m, 1H), 4.50 (AB, 2H), 4.36 (AB, 2H), 3.89 (s, 3H), 3.16 (m, 1H), 3.07 (m, 1H), 2.15 (m, 1H), 1.74 (m, 1H). FAB MS, [M+H]*=588. Elemental analysis calculated with 1.2 molecof H₂O: C=53.14%, H=4.52%, N=9.68%; found C=53.14%, H=4.24%, N=9.42%.

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The little compound is prepared from 1-(3-(6),-emitto-2-exopyrrolidin 1 yhnethyl)benzoniirile hydroun ride as in EXAMPLE 2.44 ELIMAXE; 7-

-2-[lysned(lydramonimionima)-6]-1] 7-Methoxynaphthalene-2-sulfonic acid (1-[3-(aminoiminomethyl)benzyl]-2-10 sulfo<u>atataooontalaoonta</u>

temperature under a balloon of Hz for 18 hours of The crude mixture is diluted with MeOH, filtered through a pad of Celite; washed with MeOH (2x10 mL) and concentrated in vacuo. The crude product is purified by RP-HPLC eluting in a

C-ε-nibil gradient of 10% CH₃CN/H₂O (0.1%:TFA) to 60% CH₃CN/H₂O (0.1%:TFA) and vd/20_{11c} the appropriate product fractions are liyophilized to provide the title compound as a white solid up at toubour, source ad a solid short solid. The NMR (DMSO₂d₆, 300 MHz) δ/9.29 (bs, 2H); 9:06 (bs, 2H), 8:44 (s, 1H), 8.03 (d, 1H), 7.96 (d, 1H), 7.96 (d, 1H), 7.68 (d, 1H), 7.56 (m, 3H), 7.51 (d, 1H), 7.35 (dd, 1H), 7.12 (d, 2H), 6.72 (d, 2H), 24.71; (m, 1H); 4.39 (AB; 2H); 4.26 (AE, 2H), 25, 3.90 (s, 3H), 3.10 (m, 1H); 2.95 (m, 1H); 2.10 (m, 1H), 1.70 (m, 1H). FAB MS, [M+H]*=558. Elemental analysis calculated with 1:2 mole of H₂O: C=50.61%,

H=4.42%, N=8.68%; found C=50.61%, H=4.25%, N=8.64%.

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EXAMPLE: 45-psological phine((ysnagicalia) - 1-((y-(S)-8-mbilonycos))

30 oxopyrrolidin-3-(S)-yl}(3-nitrobenzyl)amide trifluoroacetate(n-k)-tit-(S)

EXAMPLE 24. Part C. The imidate intermediate is formed over a per up to but, as a per up to but a factor over a per up to but a factor over the country product is product is product is product in the country product is product in the country product in the country product is product in the country product in the country product is product in the country product in the country product in the country product is product in the country product in the country

35 7. The title compound is prepared as described in EXAMPLE 25, Part Atusing 7-methoxynaphthalene-2-sulfonic acid:[1-(3-cyanobenzyl)-2-oxopyrrolldin-3-(S)-yl]amide as the starting material and m-nitrobenzyl bromide in place or methyl

iodide. The crude product is purified by column chromatography in 10% EtOAc/CH₂Cl₂ to afford the title compound as a solid.

¹H NMR (CDCl₃, 300 MHz) δ 8.34 (s, 1H), 8.17 (s, 1H), 8.02 (d, 1H), 7.90 (d, 1H), 7.72 (m, 3H), 7.60 (m, 1H), 7.45 (m, 4H), 7.29 (m, 1H), 7.19 (d, 1H), 4.70 (m, 1H), 4.52 (AB, 2H), 4.46 (AB, 2H), 3.94 (s, 3H), 3.17 (m, 2H), 2.41 (m, 1H), 2.00 (m, 1H).

B. 7-Methoxynaphthalene-2-sulfonic acid {1-[3-(aminoiminomethyl)benzyl]-2-oxopyrrolidin-3-(S)-yl}-(3-nitrobenzyl)amide trifluoroacetate.

- 7-Methoxynaphthalene-2-sulfonic acid [1-(3-cyanobenzyl)-2-oxopyrrolidin-3-(S)-yl]-(3-nitrobenzyl)amide is converted to the title compound as described in EXAMPLE 24, Part C.: The imidate intermediate is formed over a period of 3 days at room temperature. The amidine formation occurred upon heating at reflux for 2 hours. The crude product is purified by RP-HPLC eluting in a
- gradient of 10% CH_3CN/H_2O (0.1% TFA) to 60% CH_3CN/H_2O (0.1% TFA) and the appropriate product fractions are lyophilized to provide the title compound as a white solid. H NMR (DMSO-d₈, 300 MHz) δ 9.29 (bs, 2H), 9.18 (bs, 2H), 8.39 (s, 1H), 8.03 (m, 2H), 7.97 (d, 1H), 7.86 (d, 1H), 7.79 (d, 1H), 7.67 (d, 1H), 7.55
- 20... (m, 5H); 7.36 (dd, 1H); 4.92 (m, 1H); 4.50 (AB, 2H); 4.37 (AB, 2H), 3.89 (s, 3H), 3.15 (m, 2H), 2.15 (m; 1H); 1.80 (m, 1H). FAB MS, [M+H] +=588. Elemental analysis calculated with 0.8 mole of H₂U: C=53.74%, H=4.44%, N=9.79%; found: C=53.73%; H=4!12%, N=9.54%.
- 25. EXAMPLE: 46 (2) A nonconstruir a and source question in a succession of a construir and a

7-Methoxynaphthalene-2-sulfonic acid (1-[3-(aminoiminomethyl)benzyl]-2-30 oxopyrrolidin-3-(S)-yl](3-nitrobenzyl)amide is converted to the title compound as described in EXAMPLE 44, Part A. The crude product is purified by RP-HPLC eluting in a gradient of 10% CH₃CN/H₂O (0.1% TFA) to 60% CH₃CN/H₂O (0.1% TFA) and the appropriate product fractions are lyophilized to provide the title compound as a white solid.

35 ¹H NMR (DMSO-d₆, 300 MHz) δ 9.30 (bs, 2H), 9.19 (bs, 2H), 8.46 (s, 1H), 8.04 (d, 1H), 7.97 (d, 1H), 7.82 (d, 1H), 7.68 (d, 1H), 7.57 (m, 3H), 7.50 (g, 1H), 7.36 (dd, 1H), 7.12 (m, 1H), 7.04 (bs, 1H), 6.82 (m, 2H), 4.80 (m, 1H), 4.35 (AB, 2H),

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4.34 (AB, 2H), 3.90 (s, 3H), 3.11 (m, 1H), 2.95 (m, 1H), 2.15 (m, 4H), 1.70 (m, 4H), 2.10 (m, 4H), 2.17 (s, 4H), 3.00 (d, 4H), 7.20 (m, 4H), 7.72 (m, 3H), 7.60 (m, 4H), 7.40 (m, 4H), 7.29 (m, 4H), 7.72 (m, 3H), 7.60 (m, 4H), 7.40 (m, 4H), 7.29 (m, 4H), 7.29 (m, 4H), 7.20 (m, 4H), 7

7-Methoxynaphthalene-2-sulfonic acid [1-(3-cyanobenzyl)-2-oxopyrrolidin-3-(S)-yl]-(2-nitrobenzyl)amide. (hypodomin-6)-(ly-(3)-8 nitrobenzyl)amide. 10 The title compound is prepared as described in EXAMPLE 25; Part A using 7methoxynaphthalene-2-sulfonic acid [1-(3-cyanobenzyl)-2-oxopyrrolidin-3-(S)yllamide as the starting material and onlitropenzyl bromide in place of methyl lodide. The crude product is triturated from 50%, EtOAc/hexanes to afford the reflux for 2 hours. The crude product is puritied by King Hours. 15 1H NMR (CDC), 300 MHz) δ 8.38 (s, 1H), 8.12 (d, 1H), 7.94 (d, 1H), 7.89 (m, 2H), 7.79 (d, 1H), 7.58 (m, 2H), 7.44 (m, 3H), 7.35 (m, 1H), 7.29 (ddp1H), 7.23 (d, 1H), 4.81 (AB, 2H), 4.65 (m, 1H), 4.42 (AB, 2H), 3.94 (s, 3H), 3.17 (m. 2H), EF D ...H 2.39 (m. 1H), 2.05 (m. 1H) o ed 92.8 & (5HM 008 ... D-ORMO) FIMM H oxopyrrolidin-3-(S)-vI)-(2-nitrobenzyl)amide trifluoroacetate(S, m) 8 3 7-Methoxynaphthalene-2-sulfonic acid [1-(3-cyanobenzyl)-2-oxopyrrolidin-3-(S)-yl]-(2-nitrobenzyl)amide is converted to the title compound as described in EXAMPLE 24, Part C. The imidate intermediate is formed over a period of 5 hours at room temperature. The amidine formation occurred upon heating at 25 reflux for 2 hours. The crude product is purified by RP-HPLC eluting in a gradient of 10% CH₃CN/H₂O (0.1% TFA) to 80% CH₃CN/H₂O (0.1% TFA) and the appropriate product fractions are lyophilized to provide the title compound as a white solid. 7 Mathex/maps..natene-2-suffected acid (1-1%-landroim 30 H NMR (DMSO-d_s, 300 MHz) δ 9.27 (bs. 2H), 9.19 (bs. 2H), 8.43 (s. 1H), 8.05 (m, 3H), 7.96 (d, 1H), 7.82 (d, 1H), 7.71 (m, 1H), 7.65 (m, 1H), 7.52 (m, 5H), 7.34 (dd, 1H), 4.91 (m., 1H), 4.73 (AB, 2H), 4.36 (AB, 2H), 3.89 (s, 3H); 3.18 (m, 1H), 3.09 (m, 1H), 2.25 (m, 1H), 1.82 (m, 1H), FAB MS, [M+H]+=588. () Elemental analysis calculated with 1.7 mole of H₂O: C=52.52%, H=4.59%, 35 N=9.57%; found C=52.53%, H=4.21%; N=9.24%or ,, b CBMC PRACE H

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7-Methoxynaphthalene-2-sulfonic acid {1-[3-(aminoiminomethyl)benzyl]-2oxopyrrolldin-3-(S)-vi)-(2-aminobenzyl)amide bistrifluoroacetate.

TENDER (DIMOCLES IN MEDICAL) 7-Methoxynaphthalene-2-sulfonic acid {1-[3-(aminoiminomethyl)benzyi]-2oxopyrrolldin-3-(S)-yl}-(2-nitrobenzyl)amide is converted to the title act thound as described in EXAMPLE 44, Part A., The crude product is purified by HP-HPLC eluting in a gradient of 10% CH₃CN/H₂O (0.1% TFA) to 80% CH₃CN/H₂O (0.1% TFA) and the appropriate product fractions are lyophilized to provide the title compound as a white solid. EJAMPLE 50

¹H NMR (DMSO-d_a, 300 MHz) δ 9.28 (bs, 2H), 9.12 (bs, 2H), 8.45 (s, 1H), 8.04 10 (d, 1H), 7.96 (d, 1H), 7.83 (d, 1H), 7.68 (d, 1H), 7.55 (m, 4H), 7.36 (d, 1H), 6.98 (m, 2H), 6.65 (d, 1H), 6.47 (m, 1H), 4.79 (m, 1H), 4.33 (AB, 2H), 4.32 (AB, 2H), 3.89 (s, 3H), 3.10 (m, 1H), 2.85 (m, 1H), 2.15 (m, 1H), 1.69 (m, 1H). FAB MS, IM+H1+=558.

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Character some nascalitics of a Carton Constayl)-2-exposure defined as EXAMPLE 49. Biglipedingsebiss bhusqdys. Cl. 1 50 of behevdos a 3-[2-Oxo-3(S)-(2-phenylethenesulfonylamino)pyrrolidin-1-ylmethyl]benzamidine trifluoroacetate.

11 NAM 2000), 200 May 87 58 (a, 14) 7.52 (s. 14). A. 2-Phenylethenesulfonic acid [1-(3-cyanobenzyl)-2-oxopyrrolidin-3(S)yljamide, the antoce and in it soom the

The title compound is prepared from ?-(3-(S)-amino-2-oxopyrrolidin-1ylmethyl)benzonitrile hydrochloride as in EXAMPLE 24, Part B using trans-βstyrenesulfonyl chloride in place of 6-methoxynaphthalene-2-sulfonyl chloride.

- The crude product is triturated from 50% EtOAc/hexanes to give the titless compound as a solid. oburist p is converted to the title compound as describ
 - TH NMR (CDCI, 300 MHz) δ 7.60 (m, 1H), 7.48 (m, 9H), 6.93 (d, 1H); 5.35 (d, 190 med moch is shoot or to boned is take better sheets by the terminal cool of 1H), 4.51 (AB, 2H), 4.04 (m, 1H), 3.27 (m, 2H), 2.65 (m, 1H), 2.12 (m, 1H).
 - to trade product is purified by RP-HPLC stuting in a graniant of 3-C-03(S-03). Street in the control of the con 30 product fractions are lyophilized to provious the contract fractions are lyophilized to provious fractions are secured.

2-Phenylethenesulforic acid [1-(3-cyanobenzyl)-2-oxopyrrolidin-3(S)-yl]amide is converted to the title compound as described in EXAMPLE 24, Part C. The imidate intermediate is formed over a period of 18 hours at room temperature.

The amidine formation occurred over a period of 18 hours at room temperature. The crude product is purified by RP-HPLC eluting in a gradient of 10%

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3.7

The crude product is politied by the PPLC eloping in a madem of 10%

art (m, 1H), 7.60 (m, 3H), 7.30 (m, 4H), 7.23 (m, 1H), 4.49 (AB, 2H), 4.25 (m, 1H),

EXAMPLE 51

English the track of the track of

Ilmino-(3-(3-[7-Methoxynaphthalene-2-sulfonyl)methylaminol-2-oxo-3(S)pyrrolidin-1-vimethyllphenyl)methyllcarbamic acid ethyl ester. 11 P. 5.20 g 1.35 april

To a solution of 7-methoxy-2-napthalenesulfonic acid {1-[3-5 (aminoiminomethyl)benzyl]-2-oxo-3(S)-pyrrolidin-3-yl)methylamide trifluoroacetate (4.85 g, 8.5 mmol) in 80 mL of CH2Cl, and 5 mL of DMF is added N-methylpiperidine (2.93 g, 29.5 mmol) followed by ethyl chloroformate (0.93g, 8.5 mmol). After 1.5 hours, the solution is diluted with EtOAc. The solution is washed with H2O, saturated NaHCO and saturated NaCl. The organic layer is dried over MgSO, filtered and concentrated. The crude product is purified by column chromatography eluting with gradient of 20% CH₂Cl₂/EtOAc to 30% CH₂Cl₂/EtOAc to afford the title compound (3 g, 5.6 mmol) 10 . (Has a white solid d) 60 m (Fis Ind) Th. 8 & (ERM 008 LB C 5MG) FIMILE

¹H NMR (DMSO-d_s, 300 MHz) δ 9.02 (bs, 2H), 8.79 (s, 1H), 8.02 (d, 1H), 7.93 15 (d, 1H), 7.81 (d, 1H), 7.76 (s, 1H), 7.70 (d, 1H), 7.56 (s, 1H), 7.37 (m, 3H), 4.90 (t, 1H), 4.36 (AB, 2H), 4.00 (m, 3H), 3.87 (s, 3H), 3.11 (m, 2H), 2.66 (s, 3H), 1.94 (m, 1H), 1.70 (m, 1H). FAB MS; [M+H]+=539. Elemental analysis calculated with 0.5 mole of H₂O: C=59.22%, H=5.71%, N=10.23%, found C=59.24%, H=5.90%, N=9.78%. ta partira Kar

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EXAMPLE 52 In the 12 in 1994 Of the second second of 1995 Ales 3-[2-Oxo-3(S)-{2-(pyridin-4-ylamino)-ethanesulfonylamino}-pyrrolldin-1vlmethyll-benzamidine bistrifluoroacetate. 3. 4 Callenoxyphanyll-brandplensens.

25 As Ethenesulfonic acid [1-(3-cvanobenzvi)-2-oxobvrrolidin-3(5)-vilamide. The title compound is prepared from 3-(3-(5)-amino-2-oxopy rolidin-1ylmethyl)benzonitrile hydrochloride as in EXAMPLE 24. Part B using 2chloroethanesulfonyl chloride in place of 6-methoxynaphthalene-2-sulfonyl chloride: The crude product is purified by column chromatography in a gradient of 10% EtOAc/CH2CI2 to 40% EtOAc/CH2CI2 to afford the title 30 compound as a solid as the letter of the compound as a solid as the compound as the compound as a solid as the compound as the co 3 1H NMR (CDCI, 300 MHz) δ 7.62 (d, 1H) 7.51 (m, 3H), 6.70 (m, 1H), 6.42 (d, "1H), 6.03 (d, 1H), 5.20 (bs, 1H), 4.52 (AB, 2H), 3.99 (m, 1H), 3.25 (m, 2H), 2.62 (m, MH), 2.08 (m, 1H), 6 close 2 err . Oak bolstube one O_sH . HO, He filered, and concentrated. The colde polition is ported by column

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B. 3-[2-Oxo-3(S)-(2-(pvridin-4-vlamino) ethan esulfon vlamino) ylmethyll-benzamidine bistrifluoroacetate.

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To, a solution of ethenesulfonic acid [1-(3-cyanobenzyl)-2-oxopyrrolidin-3(S)yl]amide (0.20 g, 0.64 mmol) in 20 mL of a 1:1 mixture of THE/CH, Cl; is added 4-aminopyridine (0.20 g, 0.64 mmol). The mixture is stirred at room temperature for 18 hours, and then heated at reflux for 3 hours. The reaction mixture is allowed to cool and concentrated in vacuo. The crude 2-(pyridin-4gi an ylamino)-ethanesulfonic acid([1-(3-cyanobenzyl)-2-oxopyrrolidin-3(S)-yllamide tom: to ls converted to the title compound as described in EXAMPLE:24 Part C. The imidate intermediate is formed over a period of 18 hours at room temperature. The amidine formation occurred upon heating at reflux for 4 hours. The crude 10 product is purified by RP-HPLC eluting in a gradient of 2% CH₃CN/H₂O (0:1% TFA) to 50% CH₂CN/H₂O (0.1% TFA) and the appropriate product fractions are House a 3 lyophilized to provide the title compound as a white solid. Oracle 10.110 ¹H NMR (DMSO-d_s, 300 MHz) δ 9.47 (bs, 2H), 9.36 (bs, 2H), 8.20 (m, 3H), 8.14 re v (m, 1H), 8.10 (s, 1H); 7.71 (m, 1H); 7.63 (s, 1H), 7.59 (d, 2H) (6.80 (m, 1H), 4.61 15 (m, 2H), 4.50 (AB, 2H), 4.27 (m) 1H), 3.80 (m, 2H), (3.23 (m, 2H), 2.40 (m, 1H), 1.80 (m, 1H). FAB MS, [M+H] = 417. Elemental analysis calculated with 2.5 __be__sid_discle of H₂O: C=40.06%, H=4.53%; N=12:19%, (found) C=40.06%, H=3.68%, with C.J. mole of H.O.: C=59.22%, H=6.7191 N=10.20%, 6.865.6539 acres 기교등 유미와 이 의가임인...

20 EXAMPLE 53

2'-Methoxybiphenyl-4-sulfonic acid (1-[3-(aminoiminomethyl)benzyl]-2--- oxopyrrolidin-3(S)-yl}-amide trifluoroacetate.mpinya.--\$)-(3)\$-ox0-5-E---- etateosorouthlaid snibimascad-llydtan---

A. 4-(2-Methoxyphenyl)-bromobenzene.

To a solution of 2-bromoanisole (3.5-g. 18.7 mmol) in 40 mb of THF at -7°C is added n-butyl lithium (11.7 mL of a 1.6 M solution in THF, 18.7 mmol). The solution is stirred for 15 minutes. After this time, ZnCl₂ (20 mb of a 1M solution in Et₂O, 20 mmol) is added. The solution is allowed to warm to ambient temperature, and stirred for 3 hours. After this time, a solution of 4-365.

30 logopromobenzene (5.6 g. 19.8 mmol), and tetrakis (triphenylphosphine)- CE

palladium(0) (1.1 g, 1 mmol) in 30 mL of THF is added. The reaction mixture is stirred for 16 hours. After this time, the solution is poured into 100 mL of H₂O.

The solution is diluted with EtOAc. The organic layer is washed with 2 N

NH₄OH, H₂O and saturated NaCl. The organic layer is dried over MgSO₄.

filtered, and concentrated. The crude product is purified by column chromatography eluting with gradient of 10% CH₂Cl₂/hexanes to 20%

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CH₂Cl₂/hexanes to afford the title compound (2.61 g, 10 mmol) as a crystalline solid.

B. 2'-Methoxyhiphenyl-4-sulfonyl chloride.

To a solution of 4-(2-methoxyphenyl)bromobenzene (0.82 g, 3.2 mmol) in 15 mL of THF at 78°C is added n-butyl lithium (2 mL of a 1.6 M solution in hexanes, 3.2 mmol). After 30 minutes, the solution is transferred to a flask

- containing 10 mL of SO₂ in 40 mL of Et₂O at -78°C. The solution is stirred at -78°C for 30 minutes, and then at ambient temperature for 2 hours. After this time, the solution is concentrated. The residue is dissolved in 20 mL of hexanes. The solution is cooled to 0°C and sulfuryi chloride (3.2 mL of a 1 M solution in CH₂Cl₂) is added. The solution is stirred for 1 hour. After this time,
- the solution is concentrated. The crude product is purified by column chromatography eluting with 2% EtOAc/hexanes to afford the title compound (0.34 g, 2.6 mmol) as an oil. (0.34 g, 2.

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The title compound is prepared from 3-(3-(S)-amino-2-oxopyrrolidin-1-ylmethyl)benzonitrile hydrochloride as in EXAMPLE 24, Part B using 2'-

- 25 methoxybiphenyl-4-sulfonyl chloride in place of 6-methoxyhaphthalene-2.

 Sulfonyl chloride. The crude product is purified by column chromatography

 Seluting with algradient of 10% EtOAc/CH₂Cl₂ to 20% EtOAc/CH₂Cl₂ to give the

 String title compound as a white foam \.\(\Lambda\) \(\O(1) \) A So he had a selice product.
 - ¹H NMR (CDCl₃, 300 MHz) δ 7.95 (m, 2H); 7:48 (d; 7H); 7.08 (m; 2H); 5.51 (bs, 300 1H); 4.50 (AB; 2H); 3.88 (s; 3H); 3.26 (m, 2H); 2.62 (m, 1H), 2.19 (m, 1H). (H); 3.63 (H); 3.
 - D. 2'-Methoxybiphenyl-4-sulfonic acid (1-[3-(aminoiminomethyl)benzyl]-2-oxopyrrolidin-3(S)-yl) amide trifluoroacetate.
- 2'-Methoxybiphenyl-4-sulfönic-acid-[1-(3-cyanobenzyl)-2-oxopyrrolidin-3-(S)-35,5-yl]amide is:converted to the title compound as described in EXAMPLE 24, Part -: C: The crude product is purified by RP-HPLC eluting with a gradient of 10% and the second of the powers of ebunally-(2)-E-nit 10-yyqxx

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CH3CN/H2O (0,1%:TEA) to 60% CH3CN/H2O (0.1% TEA) and the appropriate product fractions are lyophilized to provide the title compound as a white solid. - 61 80.7 [H-NMR (DMSO-d₆₁300 MHz) δ 9.31 (bs.(4H)) 8:21 (d, 1H)) 7.90 (m, 2H), 7.61 (m, 3H), 7.41 (m, 2H), 7.35 (m, 2H), 7.12 (m, 3H), 4.45 (AB, 2H), 4.18 (m, 1H), 3.76 (s, 3H), 3.15 (m, 2H), 2.15 (m, 1H), 1.68 (m, 1H). FAB MS, $[M+H]^{+}=479$. 5 B. 21-Melnoxy/hiphenye/-sulfonyl-chloride. To a solution of 4-(2-methoxygnery)bremedenzened (greenyxy) term-S)-b to notition as of ni ni 5.6.7.8-Tetrahydrophenanthrene-3-sulfonic acid 11-13-ts 刊刊 证证 de la cominoiminomethyl)benzyl]-2-oxo-3(S)-pyrrolidin-3-yl)amide trifluoroacetate. containing 10 mL of SO, in 40 mL of Et₂O at 78°C. The solution is stinether -78 °C for 30 3.6.7.8-Tetrahydrophenanthrene-3-sulfonyl chloride. 08 101 O'88 30 5,6,7,8-Tetrahydrophenanthrene-3-sulfonic acid sodium salt (1 g:3.68 mmol) is Mark to suspended in 5 mL of thionyl chloride. DMF (2 drops) is added and the solution is heated to 60°C for 30 minutes. After this time, the reaction mixture is concentrated. The residue is triturated with CH, Cl, and the resulting solid is change filtered off of The collected organic solution is concentrated. The crude product is purified by column chromatography eluting with 10% EtOAc/hexanes to give the title compound (0,60 g,(2,3 mmol) as a white solid OCO; FIMM H ¹H NMR (CDCl₃, 300 MHz) δ 8.51 (s, 1H), 8.12 (d, 1H), 8.00 (d, 1H), 7.78 (d, 20 1H), 7.37 (d, 1H), 3.12 (m,2H), 2.98 (m, 2H), 1.98 (m, 4H). C. 21 Methorybioberyl-4-sulfonic acid 11-18-syenobenzyil-2-oxpoyrolidio 11-B. 5.6.7.8-Tetrahydrophenanthrene-3-sulfonic acid [1-(3-cvanobenzyl)-2-- oxopyrrolidin-3-(S)-vilamide.g and becase a si bruogmod elili ed? The title compound is prepared from 3-(3-(S)-amino-2-oxopyrrolldin-1-25 ylmethyl)benzonitrile hydrochloride as in EXAMPLE 24. Part By substituting 5,6,7,8-tetrahydrophenanthrene-3-sulfonyl chloride for 6-methoxynaphtnalene-2-sulfonyl chloride. The crude product is purified by column chromatoc. aphy eluting with a gradient of 20% EtOAc/CH2Cl2 to 30% EtOAc/CH2Cl2 to give the HANNER (CDC), 500 MHz) 8 1.95 m .mgol elifw a sa bruogmooellit ¹H NMR (CDCl₃, 300 MHz) δ 8.38 (s, 1H), 8, 19 (d, 1H), 7.89 (m, 1H), 7.70 (m, 1H), 7.56 (m, 1H), 7.39 (m, 4H), 5.45 (bs, 1H), 4.42 (AB, 2H), 3.76 (t, 1H), 3.19 (m, 4H), 2.99 (m, 2H), 2.58 (m, 1H), 1.94 (m, 5H), endiny and aM-S ... expuyrrolidin-3(5)-vtl emine influeroscetete.

C. 5.6.7.8-Tetrahydrophenanthrene-3-sulfonic acid (1-[3-3/xorfolf-15] (aminoiminomethyl)benzyl]-2-oxo-3(S)-pyrrolidin-3-yl}amide trifluoröacetate. 5,6,7,8-Tetrahydrophenanthrene-3-sulfonic acid [1-(3-cyanobenzyl)-2oxopyrrolidin-3-(S)-yl]amide is converted to the title compound as described in EXAMPLE 24, Part C. The crude product is purified by RP-HPLC eluting with a gradient of 10% CH₃CN/H₂O (0.1% TFA) to 60% CH₃CN/H₂O (0.1% TFA) and the appropriate product fractions are lyophilized to provide the title compound as a white solid.

¹H NMR (DMSO-d₆, 300 MHz) δ 9.31 (bs, 2H), 9.03 (bs, 2H), 8.41 (s, 1H), 8.22 (dd, 2H), 7.89 m, 1H), 7.63 (m, 4H), 7.39 (d, 1H), 4.44 (AB, 2H), 4.19 (m, 1H), 3.12 (m, 4H), 2.91 (m, 2H), 1.88 (m, 5H), 1.58 (m, 1H). FAB MS, [M+H] +=477. Elemental analysis calculated with 2.50 mole of H₂O cal. C=52.91%, H=5.39%, N=8.81% found C=52.67%, H=4.77%, N=8.41%.

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Isoquinoline-5-sulfonic acid (1-[3-(aminoiminomethyl)benzyl]-2-oxo-3(S)-pyrrolidin-3-yl}amide bistrifluoroacetate.

A. Isoquinoline-5-sulfonyl chloride.

The title compound is prepared as described in EXAMPLE 54, Part A using isoquinoline-5-sulfonic acid in place of 5,6,7,8-tetrahydrophenanthrene-3-sulfonic acid, sodium salt. The crude product is purified by triturating with Et₂O to give the product as a white solid.

; 6 20 ° ELMS, [M]+=227. (5) \$1 \$2 \$2 \$2. (4) \$2. (4) \$2. (4) \$2. (4) \$3. (4)

(A) (A) (2 (Hr, m) (A) (A) (A)

B. Isoquinoline-5-sulfonic acid [1-(3-cyanobenzyl)-2-oxopyrrolidin-3-(S)-

William Hall Minn

The title compound is prepared from/3-(3-(S)-amino-2-oxopyrrolidin-1-25 sylmethyl)benzönitrile hydrochloride as in EXAMPLE 24 Part B, substituting selection of a significant of 2% MeOH/CH₂Cl₂ to 4% MeOH/CH₂Cl₂ to give the title compound as a white foams out to spive of the allocate of a significant of 2% MeOH/CH₂Cl₂ to the significant of 2% MeOH/CH₂Cl₂ to the title compound

- 30 ; 1 H.NMR (CDCl₃/300 MHz) δ 9.38 (s; 1H), 8.81 (d, 1H), 8.49 (m, 2H), 8.22 (d, 1H), 7.70 (m, 1H), 7.56 (m, 1H), 7.41 (m, 3H), 5.77 (bs, 1H), 4.41 (AB, 2H), 3.84 (t, 1H), 3:17 (dd, 2H), 2.50 (m, 1H), 1.95 (m, 1H).
 - C. Isoquinoline-5-sulfonic acid (1-[3-(aminoiminomethyl)benzyl]-2-oxo-3(S)-pyrrolldin-3-yl)amide bistrifluoroacetate.

 Isoquinoline-5-sulfonic acid [1-(3-cyanobenzyl)-2-oxopyrrolldin-3-(S)-yl]amide is converted to the titl compound as described in EXAMPLE 24, Part C. The

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3 this product is purified by RP-HPLC eluting with a gradient of 10% CH₃CN/H₂O (0.1% TFA) to 60% CH₃CN/H₂O (0:1% TFA) and the appropriate it compound as a white solid. ¹H NMR (D₂O, 300 MHz) δ 9.74 (s, 1H), 8.92 (d, 1H), 8.77 (d, 1H), 8.63 (m, 2H), < 15 (m. 2H) 2.13 (m. 3H), 4.28 (m, 3H), 3.15 (m. 2H), 2.13 (m. 2H), 4.28 (m, 3H), 4.28 (m, 3H), 4.28 (m, 2H), 4.13 (m. 2H), 4.13 (m. 2H), 4.28 (m, 3H), 4.2 (a) 21H), 1.66 (m, 1H). FAB MS, [M+H]*=424 Elemental analysis calculated with 2 mole of H₂O cal: C=43.67%; H=3.96%; N=10.19%; found C=43.59%, H=3.34%, =3.81% found C=52,67%, H=4,77%, H=5,41% 10 EXAMPLE 56 5-Chlorothiophene-2-sulfonic acid {1-[3-(aminoiminomethyl)benzyl]-2-oxo-3(S)-pyrrolidin-3-yl)amide trifluoroacetates pinoitye-ö-enfloriupost pyrroligin-3-yllamide bistriflyorgayetate. A. 5-Chlorothiophene-2-sulfonic acid [1-(3-cvanobenzyl)-2-oxopyrrolidin-3-(S)-15 vllamide. A_ isagunoline-5-sulfanyl sincede. The title compound is prepared from 3-(3-(S)-amino-2-exopyrrolidin-1ylmethyl)benzonitrile hydrochloride as in EXAMPLE 24, Part B; substituting 5chlorothiophene-2-sulfonyl chloride for 6-methoxynaphthalene-2-sulfonyl chloride. The crude product is used without further purification: # of ¹H NMR (CDCl₃, 300 MHz) δ 7.61 (m, 1H), 7.47 (m, 4H), 7.00 (m, 1H), 5.41 (bs, 20 1H), 4.50 (AB, 2H), 3.89 (m, 1H), 3.24 (m, 2H), 2.62 (m, 1H), 2.11 (m, 1H). E. Isaguinolina-b-sulfonid aud [1-13-evalioberizy]: 2-oxonyriolidir 2 18 B. 5-Chlorothiophene-2-sulfonic acid {1-[3-(aminoiminomethyl)benzyl]-2-oxo-3(S)-pyrrolidin-3-yl}amide trifluoroacetate ചനു si bruodmon eliit ലന്ദ് 5-Chlorothiophene-2-sulfonic acid [1-(3-cyanobenzyl)-2-oxopyrrolidin-3-(S)yl]amide is converted to the title compound as described in EXAMPLE 24, Part C. The crude product is purified by RP-HPLC eluting with a gradient of 10% CH₃CN/H₂O (0.1% TFA) to 60% CH₃CN/H₂O (0.1% TFA) and the appropriate product fractions are lyophilized to provide the title compound as a white solid. 30, 1H NMR (DMSO-d_a, 300 MHz), δ 9.31 (bs., 2H), 9.12 (bs., 2H), 8.60 (σ, 1: 7.68 (m, 1H), 7,56 (m, 3H), 7.21 (m, 1H), 4.43 (AB, 2H), 4:20 (AB, 2H), 3.18 (m, 2H). 2.19 (m, 1H), 1.69 (m, 1H), FAB MS, [M+H] = 413 + Elemental analysis calculated with 0.75 mole of H₂O cal. C=40.0%, H=3.64%, N=10.37%, found C=40.04%, H=3.64%, N=10.05% It bios sincline its illustration of 35 obsteographical shapes a shilory? 63 EXAMPLE 57 COXE Select orderings to 11 bloss principles & in incremental

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2.4-Diaminoquinazoline-6-sulfonic acid (1-[3-(aminoiminomethyl)benzyl]-2-oxo-3(S)-pyrrolidin-3-yl}amide trifluoroacetate.

or the fill that the place of the field of

A. 2.4-Diaminoquinazoline-6-sulfonyl chloride sulfate salt.

To a hot solution of 2,4-diaminoquinazoline (2.3 g, 14.1 mmol) is added 2 mL of conc. H₂SO₄. The solution is further heated until all the solid dissolves. The solution is then cooled to ambient temperatures and a solid forms. The solid is filtered off. The solid is then cooled to 0°C and a suspension of 0.1 g of NaCl in 3 mL of chlorosulfuric acid is added dropwise. The resulting solution is heated to 150°C for 3 hours. After this time, the solution is poured into 50 mL of ice water, the resulting solid is collected by filtration and dried under vacuum. The title compound (3.2 g, 9 mmol) is obtained as a white solid.

¹H NMR (DMSO-d_s, 300 MHz) δ 12.50 (bs, 2H), 9.15 (bs, 1H), 8.78 (bs, 1H), 8.52 (s, 1H), 7.98 (d, 1H), 7.41 (d₃1H), some ablest of the constant of the c

nasibate atiw gnithe yngstgerseredde amulec yn beine y ai't eit ong sered B. 2.4-Diaminoguinazoline-6- sulfonic acid [1-(3-cyanôbenzýl)-2=** oxopyrrolidin-3-(\$)-yllamide.

To a solution of 3-(3-(S)-amino-2-oxopyrrolidin-1-ylmethyl)benzonitrile hydrochloride (0.50 g, 2 mmol) in 8 mL of H₂O is added triethyl amine (0.7 g, 7 mmol). After stirring for 10 minutes, 2,4-diamino-quinazoline-6-sulfonyl chloride sulfate salt (0.71 g, 2 mmol) is added. The solution is refluxed for 1 hour. After this time, the solution is cooled to ambient temperatures. The solution is filtered. The collected solid is dried under vacuum to give the title compound (0.22 g, 0.5 mmol) as a white solid an eladige of the content.

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2,4,Diamino-quinazoline-6; sulfonic acid [1-(3-cyanobenzyl)-2-oxopyrrolidin-3-[H(S)-yl]amide is converted to the title compound as described in EXAMPLE 24, Part C. The crude product is purified by RP-HPLC eluting with a gradien of 10% CH₃CN/H₂O (0.1% TEA) to 60% CH₃CN/H₂O (0.1% TEA) and the

appropriate product fractions are lyophilized to provide the title compound as a white solid.

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S-125 1H NMR (D<sub>2</sub>O; 300 MHz) δ'8.41 (s,1H), 8.08 (d,1H), 7.55 (m; 1H), 7.43 (m, 4H),
                   4.32 (AB, 2H), 4.15 (m; 1H); 3.13 (m) 2H), 2:12 (m; 1H); 1.63 (m; 1H). FAB MS,
                   [M+H]+=455. Elemental analysis calculated with 0.50 mole of H<sub>2</sub>O cal.
                   C=38.77%; H=3:25%, N=13:91%, Pfound C=38.78%; H=3:23%; N=13.92%.
   To a hot solution of 2,4-diaminoquinazoline (2.3 n, 14.1 minol) is added $\mathbf{Z}_{\circ}\in_{\circ}$
  of conc. H, SO. The setution is further heated inthe 186 BLISMAXIVES. The
 த bil நடி சுர் 7-Methoxy-2-napthalenesulfonic acidi படு (aminoiminomethy)) நடித்திரையில் முற்று முற
ਸਮੇਂ ਵਿਸ਼ਾਰ 3(S)-pyrrolidin-3-yllethylamide trifluoroacetate l bi os ed l ਮੀਂਹ benefit
 3 mill of chlorosurfuric across added dropylisa. The resulting solution to heated
       10 5 A= 7-Methoxy-2-napthalenes ulfonic acid 11-(3-cyanobenz
water, the resulting solid is collected by filtration an epimaly deflution of the
                  The title compound is prepared as described in EXAMPLE 25, Part A using 7-
       methoxynaphthalene-2-sulfonic acid [1-(3-cyanobenzyl)-2-oxopyrrolidin-3-(S)-
                  yl]amide, prepared as described in EXAMPLE 43, Part A, and ethyl iodide. The
                  crude product is purified by column chromatography eluting with gradient of
                  15% EtOAc/CH2Cl2 to 25% EtOAc/CH2Cl2 to afford the title compound as a
                  white foam.
                                                                                       exepyrrelidin-3-(S)-vllam.ne.
                3H NMR (CDCI<sub>3</sub>, 300 MHz) δ 8.46 (s, 1H), 7.92 (m, 2H), 7.81 (s, 1H), 7.50 (m,
    20 (m;:1H), 2.23 (m;:1H); 1:22:(m;:3H); 0: 10 minutes(HE:m); 20:10; (H::m)
        chickle suifate calt (0.21 q, 2 minol) is added. The solution is refluxed for 1
            B. 7-Methoxy-2-napthalenesulfonic acid (1-13-(am.noiminomethymber
      ent eroxo-3(S)-pyrrolidin-3-yllethylamide trifluoroacetate. benefit ai notinios
                 7-Methoxy-2-napthalenesülfonic acid [1-(3-cyanobenzyl)-2-oxopyrroligin-3-
      25 (S)-yl]ethylamide is converted to the title compound as described in EXAMPLE
      24 Part Co The crude product is purified by RP-HPLC eluting with a gradient of
                 10% CH<sub>3</sub>CN/H<sub>2</sub>O (0.1% TFA) to 60% CH<sub>3</sub>CN/H<sub>2</sub>O (0.1% TFA) and the
                 appropriate product fractions are lyophilized to provide the title compound as a
    C. C. Diamino-quinazoline-3-suifonic acid 11-11-(eminoim biloe, etidw, er zvic
                 <sup>1</sup>H NMR (CDCl<sub>3</sub>, 300 MHz) δ.10.24 (bs. 2H), 8.48 (sμ. 1H), 7.99 (m, 1H), 7.90 (m,
  2.00 (m, 1H), 7.79 (m, 1H), 7.53 (m, 4H), 7:26 (m, 1H), 5.08 (d, 1H), 4.29 (m, 1H), 4.08
     ுத் து (m; /1H), 3,92 (s, 3H), 3,38 (m; 2H)  ்3:20 (m; 1H)  ்2:51 (m; 2H) ்1.15 (m; 3H).
        EAB MS. [M+H]:=481: Elemental analysis calculated with 1.75 mole of H<sub>2</sub>O cal.
                C=50.39%, H=4.72%, N=8.40%; found C=49.99%, H=4.69%, N=8.12%.
   appropriate product fractions are lyopt iffeed to provine the title compound \frac{35}{100}
                EXAMPLE 59
                                                                                                                        Direct children
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7-Methoxy-2-napthalenesulfonic acid (1-[3-(aminoiminomethyl)benzyl]-2-oxo-3(S)-pyrrolidin-3-yl}(3-fluorobenzyl)amide trifluoroacetate.

A. 7-Methoxy-2-napthalenesulfonic acid [1-(3-cyanobenzyl)-2-oxopyrrolidin-3-

5 (S)-vil-(3-fluorobenzyl)amide.

The title compound is prepared as described in EXAMPLE 25, Part A using 7methoxynaphthalene-2-sulfonic acid [1-(3-cyanobenzyl)-2-oxopyrrolidin-3-(S)yl]amide, prepared as described in EXAMPLE 43, part A, and 3-fluorobenzyl bromide. The crude product is purified by column chromatography eluting with

gradient of 40% EtOAc/hexanes to 50% EtOAc/hexanes to afford the title the compound as a white foam. அ. மா மெய்யம் கங்கள் பி yxor வில்

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¹H NMR (CDCl₃, 300 MHz) δ 8.45 (s, 1H), 7.92 (m, 2H), 7.80 (d, 1H), 7.60 (m, 1H), 7.49 (m, 3H), 7.25 (m, 3H), 7.17 (m, 2H), 6.92 (m, 1H), 4.62 (m, 3H), 4.31 (m, 2H), 3.96 (s, 3H), 3.05 (m, 2H), 2.30 (m, 1H), 1.97 (m, 1H). umbd5 for, enit eni enivorr, bi pesit'rigovi ena o sinue it touborg erendourige sit

B. 7-Methoxy-2-napthalenesulfonic acid {1-[3-(aminoiminomethýl)benzyl]-2oxo-3(S)-pyrrolidin-3-yi}-(3-fluorobenzyl)amide trifluoroacetate.

7-Methoxy-2-napthalenesulfonic acid [1-(3-cyanobenzyl)-2-oxopyrrolidin-3-(S)-yl]- (3-fluorobenzyl)amide is converted to the title compound as described

> 20 In EXAMPLE 24, Part C. The crude product is purified by RP-HPLC eluting with a gradient of 10% CH₃CN/H₂O (0.1% TFA) to 60% CH₃CN/H₂O (0.1% TFA) and the appropriate product fráctions are lyophilized to provide the title compound as a white solid.

¹H NMR (DMSO-d₆, 300 MHz) δ 9.25 (bs, 4H), 8.41 (s, 1H), 7.99 (m, 2H), 7.79 _x 25 /x (m/s(H), 7.69 (m) (H), 7.51 (m, 4H), 7.24 9m, 4H), 7.04 (m, 1H), 4.80 (m, 1H). 4.38 (m, 4H), 3.88 (s, 3H), 3.08 (m 2H), 2.12 (m, 1H), 1.71 (m, 1H). FAB MS, [M+H] =561. Elemental analysis calculated with 0.25 mole of H₂O cal. \$399 \$20 C=56.60%, H=4:53%, N=8.25%, found C=56.54%, H=4:48%, N=8.18%.

The user pound is believed as described in EXAMPLE for the entire transfer in the same of the same of

7-Methoxý-2-napthalenesulfonic acid (1-13-(aminoiminomethyl)benzyll-2-oxoly as div 3(S)-pvrrolidin-3-vi)(4-methviben zvi) amide trifluoroacetate. promide. The crude product is purified by column chromatography shain, with

it right to a charge and hundred

AT 7-Methoxy-2-napthalenesulfonic acid [1-(3-cyanobenzyl)-2-oxopyrrolidin-3composed as a witte roams.

35 (S)-yl]-(4-methylbenzyl)amide.

> The title compound is prepared as described in EXAMPLE 25, Part A using 7methoxynaphthalene-2-sulfonic acid [1-(3-cyanobenzyl)-2-oxopyrrolidin-3-(S)-

ryl]amide, prepared as described in EXAMPLE 43 part A, and 4-methylbenzyl bromide, e.The crude product is purified by column chromatography eluting with gradient of 40% EtOAc/hexanes to 50% EtOAc/hexanes to afford the title -9 riplio tyo compound as a white foam as pinciluse electrone-S-yxottaM-7. A ¹H NMR (CDCl₃, 300 MHz) δ 8.43 (s, 1H), 7.92 (m, 2H), 7.78 (d, 1H), 7.57 (m, 5 posts 6 1H), 7.43 (m, 3H), 7.22 (m, 5H), 7.04(m, 2H), 4.56 (m, 3H), 4.28 (m, 2H), 3.92 (s, # -E-mibito 3H), 2.99 (m, 2H), 2.27 (m, 4H), 1.99 (m, 1H), cheladridanyxoniam yijamide, prepared as described in EXAMPLE 42 part A and 3-thordbillizyi riti v garrule B. 7-Methoxy-2-napthalenesulfonic acid (1-[3-(aminoiminomethyl)benzyl]-2-10 oxo-3(\$)-pyrrolidin-3-yl)(4-methylbenzyl)amide trifluoroacetate 7-Methoxy-2-napthalenesulfonic acid [1-(3-cyanobenzyl)-2-oxopyrrolidin-3-

(S)-yi](4-methylbenzyi)amide is converted to the title compound as described in EXAMPLE 24, Part C. SThe crude product is purified by RP-HPLC eluting with a gradient of 10% CH3CN/H2O (0.1% TFA) to 60% CH3CN/H2O (0.1% TFA) and

15 the appropriate product fractions are lyophilized to provide the title compound

B. Z-Metnoxy-2-napthalenesuffunic acid (1-12-(amiblios etides & paratrages of the control of the ¹H NMR (DMSO-d_e, 300 MHz),δ.9.29 (bs_r2H), 9.11 (bs_r2H), 8.40 (s, 1H), 7.98 2-nibites (m, 2H), 7.81 (d, 1H), 7.65 (m, 1H), 7.51 (m, 4H); 7.32 (m, 1H), 7.19 (m, 3H), ...adhassa 7,05 (du2H), 4,75 (t,1H), 4,45 (m, 2H), 4,25 (m, 2H), 3.89 (s,3H), 3.06 (m, 1H), 20 2.95 (m, 1H), 2,11 (s, 3H), 2.10 (m, 1H), 1.64 (m, 1H). FAB, MS. [M+H]+=557. Elemental analysis calculated with 2 mole of H₂O cal. C=56.08%, H=5.28%, N=7.93%, found C=56.00%, H=4.69%, N=7.73%, etalogoga entre consideration of the consideration

"HINMR (DMSC-d, 300 MHz) 6 9.25 (bs, 4H), 0.41 (s, 19.3.19MAX3 : H), 7.70

25 7-Methoxy-2-napthalenesulfonic acid {1-[3-(aminoiminomethyl)benzyl] 2-oxo-M. P. .. 3(S)-pyrrolidin-3-yl)(3-methylbenzyl)amide trifluorcacetate: m) 88.49

in all research Elemental analysis calculated with 0.25 mole of H O cal A. 7-Methoxy-2-napthalenesulfonic acid [1-(3-cyanobenzyl)-2-oxopyrrolidin-3-

The title compound is prepared as described in EXAMPLE 25, Part A using 7-30 methoxynaphthalene-2-sulfonic, acid, [1-(3-cyanobenzyl)-2-oxopyrrolidin-3-(S)yl]amide, prepared as described in EXAMPLE 43, Part A, and 3-methylbenzyl bromide. The crude product is purified by column chromatography eluting with gradient of 40% EtOAc/hexanes to 50% EtOAc/ hexanes to afford the title

compound as a white foam. Letterally suggistration (1) 18:10).

The title compound is prepayed as described between Edward Elds, Fart Aluetia na all the engine makeli element is social [14] block di til 18-2-ce alaring muscu alar

(S)-vI](3-methylbenzyl)amide,

¹H NMR (CDCl₃, 300 MHz) δ 8.44 (s, 1H), 7.92 (m, 2H), 7.78 (d, 1H), 7.58 (m, 1H), 7.42 (m, 3H), 7.23 (m, 2H), 7.09 (m, 5H), 4.55 (m, 3H), 4.28 (m, 2H), 3.92 (s, 3H), 3.02 (m, 2H), 2.25 (m, 4H), 1.95 (m, 1H).

- B.º7-Methoxy-2-napthalenesulfonic acid (1-[3-(aminoiminomethyl)benzyl]-2oxo-3(S)-pyrrolidin-3-yl)(3-methylbenzyl)amide trifluoroacetate. 7-Methoxy-2-napthalenesulfonic acid [1-(3-cyanobenzyl)-2-oxopyrrolidin-3-(S)-yl]-(3-methylbenzyl)amide is converted to the title compound as described in EXAMPLE 24, Part C. The crude product is purified by RP-HPLC eluting with 10 a gradient of 10% CH₂CN/H₂O (0.1% TFA) to 60% CH₂CN/H₂O (0.1% TFA) and the appropriate product fractions are lyophilized to provide the title compound as a white solid.
- ¹H NMR (DMSO-d_s, 300 MHz) δ 9.30 (bs, 2H), 9.19 (bs, 2H), 8.42 (s, 1H), 7.98 (m, 2H), 7.82 (d, 1H), 7.66 (m, 1H), 7.51 (m, 4H), 7.32 (m, 1H), 7.06 (m, 4H),
- 4.76 (t, 1H), 4.34 (m, 4H), 3.89 (s, 3H), 3.14 (m, 1H), 2.95 (m, 1H), 2.14 (s, 3H), 2.10 (m, 1H), 1.68 (m, 1H). FAB MS, [M+H]*=557. Elemental analysis calculated with 1.25 mole of H₂O cal. C=57.18%, H=5.16%, N=8.08%, found C=57.35%, H=4.78%, N=7.98%. 10. TATABLE CELEBACE OF A
- EXAMPLE 62 in edons your 20

7-Methoxy-2-napthalenesulfonic acid {1-[3-(aminoiminomethyl)benzyl]-2-oxo-3(S)-pyrrolidin-3-vl/napthalene-2-vlmethylamide trifluoroacetate.

A. 7-Methoxy-2-napthalenesulfonic acid [1-(3-cyanobenzyl)-25, (S)-yijnapthalene-2-yimethylamide.

The title compound is prepared as described in EXAMPLE 25, Part A using 7-methoxynaphthalene-2-sulfonic acid [1-(3-cyanobenzyl)-2-oxopyrrolidin-3-(S)-yl]amide, prepared as described in EXAMPLE 43, part A, and 2-bromomethylnaphthalene. The crude product is purified by column chromatography

eluting with gradient of 40% EtOAc/hexanes to 50% EtOAc/hexanes to afford 30 the title compound as a white foam.

1H NMR (CDCI), 300 MHz) 8 8.41 (s, 1H), 7.92 (m, 2H), 7.73 (m, 5H), 7.38 (m, 6 0 w 69H), 4.81 (AB, 1H), 4.64 (t, 1H), 4.51 (m, 2H), 4.31 (AB, 1H), 3.91 (s, 3H), 2.95 The Part (m, 2H), 2.24 (m, 1H), 1.99 (m, 1H).

B. 7-Methoxy-2-napthalenesulfonic acid {1-[3-(aminoiminomethyl)benzyl]-2oxo-3(S)-pyrrolidin-3-yl)napthalene-2-ylmethylamide trifluoroacetate.

7-Methoxy-2-napthalenesulfonic acid [1-(3-cyanobenzyl)-2-oxopyrrolidin-3-(S)-yllnapthalene-2-ylmethylamide is converted to the title compound as described in EXAMPLE 24, Part C, The crude product is purified by RP-HPLC eluting with a gradient of 10% CH₃CN/H₂O (0.1% TFA) to 60% CH₃CN/H₂O (0.1% TFA) and the appropriate product fractions are lyophilized to provide the title compound as a white solid. ¹H NMR (DMSO-d₆, 300 MHz) δ 9.31 (bs. 2H), 9.20 (bs. 2H), 8,40 (s. 1H), 7.97 (m, 2H), 7.79 (m, 3H), 7.65 (m, 1H), 7.48 (m, 10H), 4.88 (t, 1H), 4.69 (m, 1H), 4.40 (m, 3H), 3.89 (s, 3H), 3.09 (m, 1H), 2.91 (m, 1H), 2.13 (m, 1H), 1.71 (m, 1H). FAB MS, [M+H] =593. Elemental analysis calculated with 0.75 mole of H₂O cal. C=60.17%, H=4.63%, N=7.63%, found C=60.03%, H=4.83%, N=7.78%. as a white solid. EXAMPLE 63 8) 848 (0-11,165) 81.8 (NS. 20) 03.9 8 (SHIA 005 ...,b-OSMQ) AMM H 7-Methoxy-2-napthalenesulfonic acid {1-[3-(aminoniminomethyl)benzyl]-2-oxo-30 T gr. 3(S)-pyrrolidin-3-yl}(3-phenylallyl)amide trifluoroacetate. (E(1,1) 6 Encet (S)-vil-(3-phenylallyl)amide. 0=57.35%, H=4.70%, N=7.58%. The title compound is prepared as described in EXAMPLE 25, Part A using 7-methoxynaphthalene-2-sulfonic acid [1-(3-cyanobenzyl)-2-oxopyrrolidin-3-20 (S)-yl]amide, prepared as described in EXAMPLE 43, part A, and cinnamyl bromide. The crude product is purified by column chromatography eluting with gradient of 20% EtOAc/hexanes to 30% EtOAc/hexanes to afford the title compound as a white foam.

10-125 13-14 NMR (CDCl₃, 300 MHz) 8 8.44 (s, 1H), 7.90 (m, 2H), 7.79 (d, 1H), 7.50 (m, 5H), 7.28 (m, 6H), 6.43 (d, 1H), 6.20 (m, 1H), 4.71 (t, 1H), 4.40 (AB, 2H), 4.01 (m, 2H), 3.91 (s, 3H), 3.17 (m, 2H), 2.48 (m, 1H), 2.31 (m, 1H) collection (S)-yl]amide, prepared as described in EXAMPLE 3. (S)-yl]amide, prepared as described in EXAMPLE 3. (S)-yl]-2-lyznadiyalenesulfonic acid (1-13-(aminonimicon 30 Oxo-3(S)-pyrrolidin-3-yl)(3-phenylallyl)amide trifiucroacetate w polityle (16)

7-Methoxy-2-napthalenesulfonic acid [1-(3-cyanobenzyl)-2-oxopyrrolidin-3-(S)-yl](3-phenylallyl)amide is converted to the title compound as described in EXAMPLE 24, Part C. The crude product is purified by RP-HPLC eluting with a gradient of 10% CH₃CN/H₂O (0.1% TFA) to 60% CH₃CN/H₂O (0.1% TFA) and the appropriate product fractions are lyophilized to provide the title compound as a white solid.

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¹H NMR (DMSO-d_s, 300 MHz) δ 9.28 (bs, 2H), 9.0ε (bs, 2H), 8.41 (s, 1H), 7.95 (m, 2H), 7.79 (m, 1H), 7.61 (m, 2H), 7.45 (m, 3H), 7.29 (m, 6H), 6.50 (d, 1H), 6.18 (m, 1H), 4.85 (t, 1H), 4.36 (AB, 2H), 4.01 (m, 1H), 3.88 (m, 1H), 3.84 (s, 3H), 3.14 (m, 2H), 2.91 (m, 1H), 2.15 (m, 1H), 1.98 (m, 1H). FAB MS,

[M+H]⁺=569. Elemental analysis calculated with 1.75 mole of H₂O cal. C=57.18%, H=5.15%, N=7.84%, found C=57.10%, H=5.15%, N=7.58%.

THE EXAMPLE 6496 OF THE DAVIDED OF DELIGHTS A DOLLOR OF

7-Methoxy-2-napthalenesulfonic acid (1-13-(aminoiminomethyl)benzyll-2-oxo-

10 3(S)-pyrrolidin-3-yl)(3-methylbenzyl)amide trifluoroacetate. instance. The crude process a partner by column uncondrography ele-

A 7-Methoxy-2-napthalenesulfonic acid [1-(3-cyanobenzyl)-2-oxopyrrolidin-3-(S)-vI]}(3-methylbenzyl)amide.

The title compound is prepared as described in EXAMPLE 26, Part A using 7-methoxynaphthalene-2-sulfonic acid [1-(3-cyanobenzyl)-2-oxopyrrolidin-3-(S)-yl]amide, prepared as described in EXAMPLE 43, part A, and

2-bromomethylnaphthalene. The crude product is purified by column chromatography eluting with gradient of 5% EtOAc/CH₂Cl₂ to 10% EtOAc/CH₂Cl₂ to afford the title compound as a white foam.

20 1 H NMR (CDCl₃, 300 MHz) δ 8.45 (s, 1H), 7.92 (m, 2H), 7.80 (d, 1H), 7.58 (m, 1H), 7.45 (m, 2H), 7.31 (m, 4H), 7.12 (m, 3H), 4.71 (m, 1H), 4.49 (m, 2H), 4.31 (AB, 2H), 3.95 (s; 3H), 2.98 (m, 2H), 2.29 (s, 3H), 2.28 (m, 1H), 1.95 (m, 1H). On the Price (0.1% Price on the Child of the Price on the Child (0.1% Price on the Child of the

B: 7-Methoxy-2-napthalenesulfonic acid (1-13-(aminoiminomethyl)benzyl]-2-

- oxo-3(S)-pyrrolidin-3-yl}}(3-methylbenzyl)amide trifluoroacetate. 7-Methoxy-2-napthalenesulfonic acid [1-(3-cyanobenzyl)-2-oxopyrrolidin-3-(S)-yl])(3-methylbenzyl)amide is converted to the title compound as described in EXAMPLE 24, Part C. The crude product is purified by RP-HPLC eluting with a gradient of 10% CH3CN/H2O (0.1% TFA) to 60% CH3CN/H2O (0.1% TFA) and
 - the appropriate product fractions are lyophilized to provide the title compound 30 as a white solid.

¹H NMR (DMSO-d_s, 300 MHz) δ 9.25 (bs, 2H), 9.14 (bs, 2H), 8.41 (s, 1H), 8.00 (m, 1H), 7.92 (m, 1H), 7.81 (m, 1H), 7.65 (m, 1H), 7.51 (m, 4H), 7.32 (m, 2H), 7.08 (m, 3H), 4.72 (t, 1H), 4.55 (m, 1H), 4.28 (AB, 2H), 3.90 (s, 3H), 3.09 (m,

1H), 2.90 (m, 1H), 2.21 (s, 3H), 2.15 (m, 1H), 1.64 (m, 1H). FAB MS, 35 [M+H]*=557. Elemental analysis calculated with 1.75 mole of H₂O cal. C=56.44%, H=5.24%, N=7.98%, found C=56.39%, H=4.69%, N=7.69%. 171 -

'된 현시은 'DAIGO-C', 300 MHz) 리9.28, (bs. 2H), 3.05 'bs. 2P!, E.41 (s. 1위), 기가 (m. 25), 276 (m. 11), 2.61 (n. 26), 2.45 (n., 34), 2.29 (6) 34/MAX3 (4) 7-Methoxy-2-napthalenesulfonic acid {1-[3-(aminoiminomethyl)benzyl]-2-oxo-3(S)-pyrrolidin-3-yl)(2-fluorobenzyl)amide trifluoroacetate. http://dia 11411-569. Flamental analysis calculated with 1.75 mole of H₂O boll. A. 7-Methoxy-2-napthalenesulfonic acid [1-(3-cyanobenzyl)-2-oxopyrrolidin-3-(S)-v1]}(2-fluorobenzyl)amide. The title compound is prepared as described in EXAMPLE 26; Part A using 7methoxynaphthalene-2-sulfonic acid [1-(3-cyanobenzyl)-2-oxopyrolid:n-3-(S)yllamide, prepared as described in EXAMPLE 43, part A, and 2-fluorobenzyl bromide. The crude product is purified by column chromatography eluting with gradient of 5% EtOAc/CH₂Cl₂ to 10% EtOAc/CH₂Cl₂ to afford the title compound 型式直接区域 as a white foam. (S)-vill(3-maily/banzyl)amide ¹H NMR (CDCl₃, 300 MHz) δ 8.50 (s, 1H), 7.93 (m, 2H), 7.80 (m, 1H), 7.61 (m, odian 2H), 7.48 (m, 2H), 7.32 (m, 5H), 7.12 (m, 1H), 6.98 (m, 1H), 4.58 (m, 4H), 4.28 (m, 1H), 3.92 (s, 3H), 3.09 (m, 2H), 2.31 (s, 1H), 2.04 (m, 1H) 2-inconcrethylnaphthalane. The orace product in purified by B. 7-Methoxy-2-napthalenesulfonic acid {1-[3-(aminoiminomethyl)benzyl]-2oxo-3(S)-pyrrolidin-3-yl)}(2-fluorobenzyl)amide trifluoroacetate. ACHE 20, 3.7-Methoxy-2-napthalenesulfonic acid, [1-(3-cyanobenzyl)-2-oxopyrrolidin-3-(S)-yl]}(2-fluorobenzyl)amide is converted to the title compound as described in EXAMPLE 24, Part C. The crude product is purified by RP-HPLC eluting with a gradient of 10% CH₃CN/H₂O (0.1% TFA) to 60% CH₃CN/H₂O (0.1% TFA) and the appropriate product fractions are lyophilized to provide the title compound as a white solid. ¹H NMR (DMSO-d₆, 300 MHz) 8 9.28 (bs, 4H), 8.42 (s, 1H), 7.95 (m, 2H), 7.79 (m, 1H), 7.55 (m, 6H), 7.31 (m, 2H), 7.11 (m, 2H), 4.85 (t, 1H), 4.48 (m, 4H), 3.89 (s, 3H), 3.08 (m, 2H), 2.15 (m, 1H), 1.72 (m, 1H). FAB MS, [M+H]*=561. Elemental analysis calculated with 2.50 mole of H₂O cal. C=53.40%, H=4.92%, N=7.78%, found C=53.55%, H=4.28%, N=7.42%. at a thirthe solid. EXAMPLE,66 31 NMS (DMSC) 45, 800 M (21 & 9 23 (bs, 61), P.14 (b. 2-Fluorobiphenyl-4-sulfonic acid (1-[3-(aminoiminomethyl)benzyl]-2-oxi-3(S)-7.00 on 3H), 4.72 (COLD) .etalosocoulitr ebimalyhtem(ly-E-nibilorryq 가는 2.90 (m. 가기), 2.21 (s. 3H), 2.15 (m. 가게), 84 (m. 기위), ٠.

2-Fluorobiphenyi-4-sulfonyi chloride. THE THE PROPERTY OF STREET OF STREET OF STREET STREET, STREET

To a solution of 4-bromo-2-fluorobiphenyl (2.54 g, 10.1 mmol) in 50 mL of THF at -78°C is added n-butyl lithium (16.3 mL of a 1.6 M solution in hexanes, 10.1 mmol). After 0.5 hour, the solution is added to a solution of 10 mL of SO₂ in 10 mL of Et₂O at -78°C. The solution is allowed to warm to ambient temperature and stirred for another 1 hour. The solution is concentrated. The resulting solid is suspended in 40 mL of hexanes and cooled to 0°C. To the suspension is added sulfuryl chloride (10 mL of a 1 M solution in CH₂Cl₂, 10 mmol). The solution is warmed to ambient temperatures. After 1 hour, the solution is concentrated. The resulting residue is triturated with hexanes. The solution is filtered and the collected solvent is concentrated. The resulting solid is recrystallized from hexanes to give the title compound (0.6 g, 2.2 mmol) as a white solid.

14 NMR (CDCl₃, 300 MHz) δ 7.88 (m, 2H), 7.68 (m, 1H), 7.52 (m, 5H).

<u>15 က B.- 2-Fluorobiphenyl-4-sulfonic acid [1-(3-cyánobenzyl)-2-oxopyrrolidin-3-(S)-yl]amide.</u>

The title compound is prepared from 3-(3-(S)-amino-2-oxopyrrolidin-1-ylmethyl)benzonitrile hydrochloride as in EXAMPLE 24, Part B, substituting 2-fluorobiphenyl-4-sulfonyl chloride for 6-methoxynaphthalene-2-sulfonyl

20 chloride. The crude product is purified by column chromatography eluting with gradient of 15% EtOAc/CH₂Cl₂ to 30% EtOAc/CH₂Cl₂ to afford the title

18. (*C. - 2:Fluorobiphenŷl-4-súlfônic àcid [1-(3-cyanobenzyl)-2-oxopyrrölidin-3-(S)yl]-methylamide 2.2 (3:1-10) (-2.2 (3:2-2) (3:2-2) (3:3-2) (3:3-2)

The title compound is prepared as described in EXAMPLE 26, Part A using 2fluorobiphenyl-4-sulfonic acid [1-(3-cyanobenzyl)-2-oxopyrrolidin-3-(S)-

yl]amide and methyl iodide. The crude product is purified by column chromatography eluting with gradient of 10% EtOAc/CH2Cl2 to 20% EtOAc/CH2Cl2 to afford the title compound as a white foam.

2H), 3.28 (m, 2H), 2.81 (s, 3H), 2.42 (m, 1H), 2.08 (m, 1H), 4.93 (t, 1H), 4.55 (AB, 2H), 3.28 (m, 2H), 2.81 (s, 3H), 2.42 (m, 1H), 2.08 (m, 1H), 4.93 (t, 1H), 4.55 (AB, 2H), 3.28 (m, 2H), 2.81 (s, 3H), 2.42 (m, 1H), 2.08 (m, 1H), 4.93 (t, 1H), 4.55 (AB, 2H), 3.28 (m, 2H), 2.81 (s, 3H), 2.42 (m, 1H), 2.08 (m, 2H), 4.93 (t, 1H), 4.55 (AB, 2H), 4.93 (t, 1H), 4.93 (t, 1H), 4.55 (AB, 2H), 4.93 (t, 1H), 4.93 (t, 1H), 4.55 (AB, 2H), 4.93 (t, 1H), 4.93 (t, 1H), 4.55 (AB, 2H), 4.93 (t, 1H), 4.93 (t, 1H),

D. 2-Flüorobiphenyl-4-sulfonic acid (1-[3-(aminoiminomethyl)benzyl]-2-oxo-3(S)-pyrrolidin-3-yl))methyamide trifluoroacetate.

41-13-cyanobenzyl)-2-oxopyrrolidin-3-(S)-yl]methylamide is converted to the title compound as described in EXAMPLE 24, on the Part C. The crude product is purified by RP-HRLC eluting with a gradient of 00.1% TFA) and the 5, appropriate product fractions are lyophilized to provide the title compound as a solid is suspended in 40 mL of hexunes and cooled to bilos ejidwa sus render 1H NMR-(DMSO-d_{ei/3}00 MHz) δ 9.39 (bs) 2H), 9.14 (bs) 2H), 7:79 (m, 3H), 7.55 (m, 9H), 4.95 (t, 1H); 4.43 (AB, 2H); 3.20 (m; 2H), 2.72 (s, 3H); 2!10 (m, 1H). 3. nobeline et. 1.93 (m, 1H). FAB MS, [M+H]*=481ser gnilluser and incremensones filtered and the collected solvent is concentrated. The reculting soft in 137 recrystallized from hexanes to give the title compound 124 19 AXX Juno 11 see a 3-[{1-[3-(Aminoiminomethyl)benzyl]-2-oxopyrrolidin-3(S)-3-yl}-(7-14) methoxynaphthalene-2-sulfonyl)amino]propionamide trifluoroacetate.

15 A. 3-[[1-(3-Cyanobenzyl)-2-oxopyrrolidin-3-(S)-yl]-7-methoxynaphthalene-2sulfonvlaminol-N-propionic acid t-butyl ester.

To a solution of 7-methoxynaphthalene-2-sulfonic acid [1-(3-cyanobenzvi)-2oxopyrrolidin-3-(S)-yllamide, prepared as described in EXAMPLE 43, part A, (0.82 g,1.9 mmol) in 10 mL of DMF is added K2CO (0:52 g/3:8 mmol) and tbutyl acrylate (0.48 g, 3.8 mmol): The solution is heated to 60°C and stirred for 24 hours. After this time, the solution is cooled to ambient temperatures and diluted with EtOAc. The solution is washed with 1 N HCl and saturated NaCl. 84 The organic layer is dried over MgSO4, filtered) and concentrated. The title compound (0.64, gaz 11 mmol) is obtained as a white foam.) 88.8 (HS ¹H NMR (CDCl₃, 300 MHz) δ 8.41 (s, 1H), 7.89 (m, 2H), 7.80 (m, 1H), 7.56 (m, 4H), 7.23 (m, 2H), 4.71 (t, 1H), 4:50 (AB, 2H), 3.92 (s; 3H); 3.63 (m, 4H), 3.37 (m, 1H), 3.36 (m, 4H), 2.78 (m, 2H), 2.41 (m, 1H), 2.20 (m, 1H) 1:42 (s, 9H).

The title courpound is prepared as described to EXAMPLE 26, Part 1 B. 3-[{1-(3-Cyanobenzyl)-2-oxopyrrolidin-3-(S)-yl}-7-methoxynaphthalene-2vijamide at dinethyl ic. ide. The crubias ainoigorg-N-lonimalynoflus 3-[{1-(3-Cyanobenzyl)-2-oxopyrrolidin-3-(S)-yl}-7-methoxynaphthalene-2sulfonylamino]-N-propionic acid t-butyl ester is converted to the title compound as described in EXAMPLE 26, Part B. The title compound is obtained as a white foam. (Hr. m) 80 s (Hr. m) 32.5 (Hs. s) 18.5 (Hs. m) 89.8 (Hs. s) 18.5 (Hs. m) 80.5 (Hs. s) 18.5 (Hs. s ¹H NMR (CDCl₃, 300 MHz) δ 8.41 (s, 1H), 7.89 (d, 1H), 7.80 (m, 2H), 7.56 (m, 35 4H), 7.22 (m, 2H), 4.74 (t, 1H), 4.50 (AB, 2H), 3.92 (s, 3H), 3.56 (m, 1H), 3.37 (m, 1H), 3.22 (m, 2H), 2.89 (m, 2H), 2.39 (m, 2H), 2.10 (m, 1H).

C:3-[(1-(3-Cyanobenzyl)-2-oxopyrrolidin-3-(S)-yl}-7-méthoxynaphthale.ne-2-sulfonylaminolpropionamide.

To a solution of 3-[{1-(3-cyanobenzyl)-2-oxopyrrolidin-3-(S)-yl}-7-

rong of the graph of the first of the first

- methoxynaphthalene-2-sulfonylamino]-N-propionic acid (0.51 g, 1 mmol) and triethyl amine (0.12 g, 1.2 mmol) in 10 mL of THF at -20°C is added ethyl chloroformate (0.11 g, 1 mmol). The solution is stirred for 15 minutes. After this time, 14.8 N ammonium hydroxide (0.1 mL, 1.5 mmol) is added. The solution is allowed to warm to ambient temperatures. The reaction is stirred for 16 hours.
- After this time, the solution is diluted with EtOAc. The organic layer is washed with 1.N.HCl, 10% Na₂CO₃ and saturated NaCl. The organic layer is dried over MgSO₄, filtered, and concentrated. The title compound (0.39 g, 0.77 mmol) is obtained as a white foam. Since the latter of the latt
- 15 £ 3H), 5.94 (bs, 1H), 5.34 (bs, 1H), 4.75 (t, 1H), 4.45 (AB, 2H), 3.92 (s, 3H), 5.51 (m, 1H), 3.40 (m, 1H), 3.19 (m, 2H), 2.78 (m, 2H), 2.32 (m, 1H), 2.09 (m, 1H).

D. 3-[{1-[3-(Aminoiminomethyl)benzyl]-2-oxopyrrolidin-3(S)-3-yl}-(7-methoxynaphthalene-2-sulfonyl)aminojpropionamide trifluoroacetate.

- 3-[{1-(3-Cyanobenzyl)-2-oxopyrrolidin-3-(S)-yl}-7-methoxynaphthalene-2-sulfonylamino]propionamide is converted to the title compound as described in EXAMPLE 24, Part C. The crude product is purified by RP-HPLC eluting with a gradient of 10% CH3CN/H2O (0.1% TFA) to 60% CH3CN/H2O (0.1% TFA) and the appropriate product fractions are lyophilized to provide the title compound 25 as a white solid. How the compound as a white solid. How the compound the solid. How the compound the c
- (m, 2H), 7.73 (m, 2H), 7.58 (m, 4H), 7.38 (m, 2H), 6.82 (m, 1H), 4.80 (t, 1H), 4.42 (AB, 4H), 3.88 (s, 3H), 3.22 (m, 4H), 2.52 (m, 2H), 2.12 (m, 1H), 1.81 (m, 1H). FAB MS, [M+H] = 678: Elemental analysis calculated with 2:25 mole of H₂O cal.
 - 30 C=49.59%, H=5.13%, N=10.33%, Foorbod (\$\frac{1}{2}\f

まはStiteting Ziff (3-Cyadet Unity) Zidvioty rolidin Sif(S)-86:国MAMAE と

-(2) /2-[{1+[3+(Aminoiminomethýl)benzyl]-2-oxopýrrolidin-3-(S)-ýljnalýhthalene-2pana- rsulfonýlamino]-N-phenethýlacetamide triflivoroacetate.

35

A. Naphthalene-2-sulfonic acid [1-(3-cyanobenzyl)-2-oxopyrrolidin-3-(S)-yllamide

The title compound is prepared from 3-(3-(S)-amino-2-oxopyrrolidin-1ylmethyl)benzonitrile hydrochloride as in EXAMPLE 24/Part B. sûbstituting naphthalene-2-sulfonyl chloride for 6-methoxynaphthalene-2-sulfonyl chloride. The title compound is obtained as a white solid.)]-8 to motion a of 5 1H, NMR (CDCI₃, 300 MHz) δ 8.47 (s,s1H), 7.92 (m, 4H); 7.61 (m; 3H); 7.42 (m, chiproformate (0.11 g. 1 minol). The solution is stirred for 15 (Htum). After this bind, 14.8 Mianneceum hydroxida (0.1 int., 1.5 inmel) is edged. The solution is a unit of B., 2-[(1-(3-Cyanobenzyl)-2-oxopyrrolidin-3-(S)-yl]naphthalene-2-015 After this time, the solution retended to the second section of the second section and the second section and the second section and the second section sectio The title compound is prepared as in EXAMPLE 26 Part A substituting naphthalene-2-sulfonic acid [1-(3-cyanobenzyl)-2-oxopyrrolidin-3-(S)-yllamide for 6-methoxynaphthalene-2-sulfonic acid [1-(3-cyanobenzyl)-2-oxopyrrolidin-3-(S)-yllamide. (The title compound is obtained as a white solid MV 14 1H NMR (CDCI₃₀300 MHz) δ 8,52 (s, 1H), 7,92 (m, 3H), 7,81 (d) 1H); 7.61 (m, (Hr. m3H), 7.42 (m, 3H), 4.61 (t, 1H); 4.42 (AB-2H), 4.12 (m, 1H); 3.78 (m, 1H), 3.21 (m, 2H), 2.60 (m, 1H), 2.41 (m, 1H), 1.42 (s, 9H). D. 3-3(1-(3-(A-ainc ininomethylipenzyll-2-oxopyrrolldin-3(S)-3-yl)-(7 2-[{1-(3-Cyanobenzyl)-2-oxopyrrolidin-3-(S)-yl)naphthalene-2-tem 20 sulfonylamino]-N-acetic acid.s-nibilaryly-2-oxopyrrolidin-s.bias acid.s-lift-(3-Cyanobenzyl)-2-oxopyrrolidin-s.bias acid.s-lift-(3-Cyanobenzyl)-2-oxopyrrolidin-s-bias acid.s-nibilaryly-2-oxopyrrolidin-s-bias acid.s-nibilaryly-2-oxopyrrolidin-s-nibilaryly-2-oxopyrrolidin-s-bias acid.s-nibilaryly-2-oxopyrrolidin-s-bias ac The title compound is prepared as in EXAMPLE 26, Part B using 2-[(1-(3cyanobenzyl)-2-oxopyrrolidin-3-(S)-yl)naphthalene-2-sulfonylaminol-N-acetic acid tert-butyl ester as the starting material. The title compound is obtained as the appropriate product fractions are lyophilized to provide the billing of the com-¹H NMR (CDCl₃, 300 MHz) δ 8.49 (s, 1H), 7.96 (m, 2H), 7.62 (m, 3H), 7.49 (m, (AB) 2H), 7.20 (m, 2H), 5.61 (bs, 4H), 4.78 (tr, 1H); 4.50 (AB, 2H), 3.90 (AB) 2H), 3.29 96. b. 1011 (m. 2H), 2.41 (m. 1H), 2.11 (m. 1H). (H) (m) 86. C. (HS, m) 87.7 (HS, m) (AEC 44), 3.88 (s. 341), 3.27 (m. 44), 2.52 (m, 24), 2.12 (m. 18), 1.84 (m. 45) D. 2-[(1-(3-Cyanobenzyl)-2-oxopyrrolidin-3-(S)-yl)naphthalene-2- 3A-1 30, ... sulfonylamino]-N-phenethylacetamideາຄວາງາະທຸກາຄາດ=H ,ລາຍາ.d=H ,ລາຍຕົວວະເປ Uè The title compound is prepared as described in EXAMPLE 26, Part C substituting 2-[{1-(3-Cyanobenzyl)-2-oxopyrrolidin-3-(S)-yl}naphthalene-2sulfonylamino]-N-acetic acid for 2-[{1-(3-cyanobenzyl)-2-oxopyrrolidin-3-(S)yl}-6-methoxynaphthalene-2-sulfonylamino]-N-acetic acid. The title compound 35 is obtained as a white foam. ćċ

A. Stabilitation 2 sulfanciacid Lefts aggrees als 2 and realities of the visits of the

 1 H NMR (CDCl₃, 300 MHz) δ 8.48 (s, 1H), 7.93 (m, 4H), 7.58 (m, 6H), 7.16 (m, 5H), 5.61 (bs, 1H), 4.58 (m, 1H), 4.40 (m, 2H), 3.80 (AB, 2H), 3.27 (m, 4H), 2.63 (m, 2H), 2.21 (m, 2H).

- 5 E. 2-[(1-[3-(Aminoiminomethyl)benzyl]-2-oxopyrrolidin-3-(S)-yl]naphthalene-2-sulfonylamino]-N-phenethylacetamide trifluoroacetate.

 The title compound is prepared as described in EXAMPLE 24, Part C using 2-[(1-(3-cyanobenzyl)-2-oxopyrrolidin-3-(S)-yl]naphthalene-2-sulfonylamino]-N-phenethylacetamide as the starting material. The crude product is purified by
- 10 RP-HPLC eluting in a gradient of 10% CH₃CN/H₂O (0.1% TFA) to 60% CH₃CN/H₂O (0.1% TFA) and the appropriate product fractions are lyophilized to provide the title compound as a white solid. A second to provide the title compound to provide the t
- 15 3.70 (m, 3H); 3.18 (m, 4H), 2.59 (m, 2H), 2.05 (m, 2H). FAB MS, [M+H]*=584. Elemental analysis calculated with 1.75 mole of H₂O cal. C=56.00%. H=5.18%, N=9.60%, found C=56.15%, H=4.84%, N=9.27%.

(8) FIRE EXAMPLE 69 Symptomatically St. of the Laboration and the companion of the companio

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- The title compound is prepared from 3-(3-cyanobenzyl)-2-oxopyrrolidin-3-(S)-yl]amide
 - ylmethyl)benzonitrile hydrochloride as in EXAMPLE 24, Part B, substituting biphenyl-4-sulfonyl chloride for 6-methoxynaphthalene-2-sulfonyl chloride.

 The title compound is obtained as a white foam sale of the substituting the substitution that substituting the substitution that substituting the substitution that substituting the substitution that substitution the substitution
- B: 2-[(1-(3-Cyanobenzyl)-2-oxopyrrolidin-3-(\$)-yl}biphenyl-4-sulfunylaminoj-N-acetic acid t-butyl ester. bike oldwa as bruognob estrent ebivolit
- 35 The title) compound is prepared as in EXAMPLE 26, Part A substituting 35 blphenyle4-sulfonic/acid-[1-(3-cyanobenzyl)-2-oxopyrrolidin-3-(S)-yl]amide for 6-methoxynaphthalene-2-sulfonic acid [1-(3-cyanobenzyl)-2-oxopyrrolidin-3-(S)-yl]amide. The title compound is obtained as a white foam.

② (m, 2H), 7.52 (m, 4H), 7.31 (m, 2H), 7.66 (m, 2H), 7.52 (m, 4H), 7.31 (m, 2H), 7.54 (m, 2H), 4.45 (m, 3H), 4.08 (AB, 1H), 3.79 (AB, 1H), 3.18 (m, 2H), 2.52 (m, 1H), 2.31 (m, 1H), 1.41 (s, 9H).

N-acetic acid.) step concerting as in EXAMPLE 26, Part Brusing 24[(1-(3-The title compound is prepared as in EXAMPLE 26, Part Brusing 24[(1-(3-Cyanobenzyl)-2-oxopyrrolidin-3-(S)-yl)biphenyl-4-sulfonylamino]-Wacetic acid starting material. The title compound is obtained as a white 10 setom. ART 301.0 0.14400.140 set to the beautiful in the title compound of 1914-98 or the starting material. The title compound of 1914-98 or the starting material. The title compound is obtained as a white 10 setom. ART 301.0 0.14400.140 set to the beautiful in the provide 0.1914-98 or the starting material. The title compound is obtained as a white 10 setom. ART 301.0 0.14400.140 set to the beautiful in the provide 0.1914-98 or the beautiful of the provide 0.1914-98 or the provide of the provide 0.1914-98 or the beautiful of the provide 0.1914-98 or the

her illidgov ការស្រើស្រីបូម្នាន់ 200 MHZ) ខ. 2924 (៣; 2H); 7.74 (៣; 3H), 7.52" (៣) 8H); 7.21 (៣, 1H), 4.61 (t, 1H), 4.52 (AB, 2H); 3.91 (AB, 2H); 3.30 (m, 2H), 2:48 (m; 1H), 2.09 ጉጋ ታ ነተ ነ (៣, বুંં H), (মুড, ಪ್ರಕ್ರಿ) ይደር (HS, ed) የ8.83 (ছেম ৩২০ বুঁচ ೧୯୯୯) সামার ৪৮

(b), 5H), 7 39 (m, 6H), 7.20 (m, 4H), 7.38 (m, 2H), 6.85 (t, 4H), 4.42 (AS, 4H)

- 15 D. 2-[(1-(3-Cyanobenzyl)-2-oxopyrrolidin-3-(S)-yl]blphenyl-4-sulfonylamino]N-phenethylacetamide.alom 37 individual betalindisc assigned in example.

 The title compound is prepared as described in EXAMPLE 26, Part C substituting 2-[(1-(3-Cyanobenzyl)-2-oxopyrrolidin-3-(S)-yl]-biphenyl-4-sulfonylamino]-N-acetic acid for 2-[(1-(3-cyanobenzyl)-2-oxopyrrolidin-3-(S)-yl]-biphenyl-4-sulfonylamino]-
 - 20 h-yll-6-methoxynaphthalene-2-sulfonylamino]-N-acetic acid. The title compound is obtained as a white foam: solven section or old νι- ο πισείνηστα που η ΝΑΒ (CDCI₃, 300 MHz) δ 7.94 (m, 3H), 7.71 (m, 3H), 7.50 (m, 7H), 7.20 (m, 5H), 4.61 (m, 1H), 4.44 (m, 3H), 3.78 (AB) 2H), 3.30 (m, 3H), 2.71 (m/3H), 2.24 (m, 2H), 2.23 doning (S)-5)-5 mon bersong σ Σουρομικώ ellit efficiency
 - 25 year and structure of the structure as in EXAMPLE 24, Part of the structure of the struc
 - phenethylacetamide as the starting material. The crude product-is purified by RP-HPLC eluting in a gradient of 10% CH₃CN/H₂O (0.1% TFA) to 60% CH₃CN/H₂O (0.1% TFA) and the appropriate product fractions are lyophilized to

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35 5H), 7.45 (m, 3H), 7.19 (m, 5H), 4.68 (m, 2H), 4.39 (m, 1H), 3.82 (AB,2H), 2.70 (m, 3H), 2.32 (m, 1H), 2.15 (m, 1H), FAB,MS, [M+H]*=610an (content a

EXAMPLE 70 Section And Leading Section 1997

2-{{1-[3-(Aminoiminomethyl)benzyl]-2-oxopyrrolidin-3-(S)-yl}-7-11methoxynaphthalene-2-sulfonylaminol-N-phenethylacetamidé trifluoroacetate.

A. 2-[{1-(3-Cyanobenzyl)-2-oxopyrrolidin-3-(S)-vl}-7-methoxynaphthalene-2sulfonylamino]-N-acetic acid t-butyl ester.

The title compound is prepared as described in EXAMPLE 26, Part A substituting 7-methoxynaphthalene-2-sulfonic acid [1-(3-cyanobenzyl)-2oxopyrrolidin-3-(S)-yljamide, prepared as described in EXAMPLE 43, part A,

for 6-methoxynaphthalene-2-sulfonic acid [1-(3-cyanobenzyl)-2-oxopyrolidin---- ::::3-(S)-yl]amide.: The title compound is obtained as a white foam. ¹H NMR (CDCl₃, 300 MHz) δ 8.41 (s, 2H), 7.81 (m, 3H), 7.50 (m, 1H), 7.44 (m, 3H); 7.22 (m; 2H); 4.61 (t, 1H); 4.42 (AB, 2H), 3.90 (s, 3H); 3.74 (AB; 1H), 3.20

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B. 2-[{1-(3-Cyanobenzyl)-2-oxopyrrolidin-3-(\$)-yl}-7-methoxynaphthalene-2-

The title compound is prepared as described in EXAMPLE 26, Part B using 2-[{1-(3-cyanobenzyl)-2-oxopyrrolidin-3-(S)-yl}-7-methoxynaphthalene-2-

20 sulfonylamino]-N-acetic acid t-butyl ester as the starting material. The title compound is obtained as a white foam more neighbor to be sufficiently to the ¹H NMR (CDCl₃, 300 MHz) δ 9.45 (bs, 1H), 8.41 (s, 2H), 7.91 (d, 1H), 7.80 (d, 1H), 7.71 (m, 1H), 7.62 (m, 1H), 7.59 (m, 3H), 7.20 (m, 1H), 4.81 (t, 1H), 4.50 (AB, 2H), 3.90 (s, 3H), 3.89 (AB, 2H), 3.28 (m, 2H), 2.41 (m, 1H), 2.16 (m, 1H). EXAMINATE 70, Part B. 101.2 [[14(B-cyanubenzy)]-2 axopyrrolidin-3-(S)-1.25

@-2-[{1-(3-Cyanobenzyl)-2-oxopyrrollidin-3-(S)-yl)-7-methoxynaphthalene-2-പര്യം a sulfonylamino]-N-phenethylacetamide na lyttlenatt, 151 അവർത്തുർ

The title compound is prepared as described in EXAMPLE 26, Part C a: da substituting 2 [[1=(3-cyahobenzyl)-2-oxopyrrolidin-3=(s)-yl)-7-

30 (Himethoxynaphthalene-2-sulfonylamino]-N-acetic acid for 2-[[1-(3-cyanobenzyl)-2-oxopyrrolidin-3-(S)-yl}-6-methoxynaphthalene-2-sulfonylamino]-N-acetic acid. The title compound is obtained as a white foam.

¹H NMR (CDCl₃, 300 MHz) δ 8.35 (m, 1H), 8.14 (m, 2H), 7.82 (m, 4H), 7.53 (m. 35H), 7.21; (m, 4H); 5:71((bs, 4H), 4.58 (AB, 1H), 4.42 (m, 2H), 3.91 (s, 3H), 3.80

(35 is (AB) 2H), 3.31 (m, 4H), 2.69 (m, 2H), 2.29 (m, 1H), 2.14 (m, 1H), (1 h)

111-(3-3) another zyl) 2 exopyrolide 3-(5) yl) -/- mattoxy schthalege > authoritylarano). History acotamide acitiro stantagima, si ti i i til i crude gi i ikini te

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D. 2-[{1-[3-(Aminoiminomethyl)benzyl]-2-oxopyrroiidin-3-(S)-yl}-6-
methoxynaphthalene-2-sulfonylaminol-N-phenethylacetamide trifluoroacetate,
The title compound is prepared as described in EXAMPLE 24; Part C using
2-[{1-(3-cyanobenzyl)-2-oxopyrrolidin-3-(S)-yl}-7-methoxynaphthalene-2-
sulfonylamino]-N-phenethylacetamide as the starting material. 1-The crude
product is purified by RP-HPLC eluting in a gradient of 10% CH ₃ CN/H ₂ O (0.1%
TFA) to 60% CH-CN/H-O (0.1%:TFA) and the appropriate product fractions are

5, sulfonylamino]-N-phenethylacetamide as the starting material. The crude product is purified by RP-HPLC eluting in a gradient of 10% CH₃CN/H₂O (0.1% TFA) to 60% CH₃CN/H₂O (0.1% TFA) and the appropriate product fractions are lyophilized to provide the title compound as a white solid of the title compound as a White soli

10 (m, 1H), 8.02 (m, 2H), 7.74 (m, 2H), 7.58 (m, 2H), 7.21 (m, 5H), 4.80 (t, 1H), 4.44 (AB, 2H), 3.85 (s, 3H), 3.84 (m, 1H), 3.58 (m, 1H), 3.21 (m, 2H), 2.64 (m, 2H), 2.15 (m, 1H), 1.99 (m, 1H). FAB MS, [M+H]*=6140 Elemental analysis calculated with 2.50 mole of H₂O cal. C=54.40%, H=5.35%, N=9.06%, found C=56.26%, H=4.87%; N=8.69%; (H), m, 34.2 (F.5.4.40%, BC), (NS, m)

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EXAMPLE 71_{n-1-(iv-(2)-8-mbile_vqoxe-S-(lysnoc-nevC-C-11-S-d-C-11-}

20. A. 2-[(1-(3-Cyanobenzyl)-2-oxopyrrolidin-3-(i) stredonay(n-6)-1);
20. A. 2-[(1-(3-Cyanobenzyl)-2-oxopyrrolidin-3-(S)-yl]-7-methoxynaphthalene-2-sulfonylamino]-N-ethylacetamide. I stridy a calibation do all branca root.

The title compound is prepared as described in EXAMPLE 26; Part C

(substituting 2-[(1-(3-cyanobenzyl)-2-oxopyrrolidin-3-(S)-yl]-7-7-7-11-11

methoxynaphthalene-2-sulfonylamino]-N-acetic acid, prepared as in a

EXAMPLE 70, Part B, for 2-[{1-(3-cyanobenzyl)-2-oxopyrrolidin-3-(S)-y₁}-6-1 methoxynaphthalene-2-sulfonylamino]-N-acetic acid and ethyl amine hydrochloride for phenethyl amine in The title compound is obtained as a white foam. 193 31-1444 (3 of bediesch as the same 13 to bound 100 entre 11 h NMH (CDCl₃, 300 MHz) δ 8.39 (s; 11H), 7.91 (m, 1H); 7.81 (m, 2H), 7.55 (m,

30 3H), 7.29 (m, 4H), 5.71 (bs, 1H), 4.50 (m, 3H), 3.93 (s, 3H); 3.80 (AB, 2H), 3.21 (m, 4H), 2.31 (m, 2H), 0.90 (m, 3H), σομέση ο έχειξειτίστας σχονά

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B. 2-[(1-[3-(Aminoiminomethyl)benzyl]-2-oxopyrrolidin-3-(S)-yl)-7-4 B'

methoxynaphthalene-2-sulfonylaminol-N-ethylacetamide trifluoroacetate.

The title compound is prepared as described in EXAMPLE 24, Part C using 2-[{1-(3-cyanobenzyl)-2-oxopyrrolldin-3-(S)-yl}-7-methoxynaphthalene-2-sulfonylamino]-N-ethylacetamide as the starting material. The crude product is

purified by RP-HPLC eluting in a gradient of 10% CH_3CN/H_2O (0.1% TFA) to 60% CH_3CN/H_2O (0.1% TFA) and the appropriate product fractions are lyophilized to provide the title compound as a white solid.

¹H NMR (DMSO-d₆, 300 MHz) δ 9.26 (bs, 2H), 9.00 (bs, 2H), 8.42 (s, 1H), 8.11 (m, 1H), 8.01 (m, 2H), 7.78 (m, 1H), 7.68 (m, 1H), 7.52 (m, 3H), 7.33 (m, 1H), 4.80 (t, 1H), 4.44 (AB, 2H), 3.89 (s, 3H), 3.71 (AB, 2H), 3.19 (m, 2H), 3.02 (m, 2H), 2.09 (m, 2H), 0.90 (m, 3H). FAB MS, [M+H]*=538. Elemental analysis calculated with 2.25 mole of H₂O cal. C=50.32%, H=5.31%, N=10.12%, found C=50.21%, H=4.59%, N=9.60%.

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A. 2-[{1-(3-Cyanobenzyl)-2-oxopyrrolidin-3-(S)-yl}-7-methoxynaphthalene-2-sulfonylamino]-N.N-dimethylacetamide in EXAMPLE 26, Part C substituting 2-[{1-(3-cyanobenzyl)-2-oxopyrrolidin-3-(S)-yl}-7-(S)-yl}-7-(S)-yl]-7-

- 20 EXAMPLE 70, Part B, for 2-[{1-(3-cyanobenzyl)-2-oxopyrrolidin-3-(S)-yl}-7-methoxynaphthalene-2-sulfonylamino]-N-acetic acid and dimethyl amine hydrochloride for phenethyl amine. The title compound is obtained as a white foam, according summarized mask in the problem of the compound of the compound
- 25 1H NMR (CDCl₃,300 MHz) & 8.49 (s;4H), 7.88 (m;4H); 7.78 (m;1H); 7.45 (m, 25 1.5H), 7.30 (m;3H); 7.4.60 (m,2H); 4.32 (m;1H); 4.20 (m;2H); 3.92 (s;3H); 3.15 (m;2H), 3.00 (s; 3H); 2.91 (s;3H), 2.28 (m;12H); 4.60 (m;2H); 4.60

¹H NMR (DMSO-d_e, 300 MHz) δ 9.22 (bs, 2H), 9.02 (bs, 2H), 8.43 (s, 1H), 7.92 (m, 2H), 7.78 (d, 1H), 7.65 (m, 1H), 7.51 (m, 4H), 7.32 (m, 1H), 7.33 (m, 1H),

4.71- (t, 1H), 4.38 (m, 3H), 3.91 ((m, 1H), 3.90 (s, 3H), 3.12 (m, 2H), 2.98 (s, 3H), 2.78 (s, 3H), 2.18 (m, 2H), 5.88 MS. [M+H]t=538. Elemental analysis of calculated with 2.25 mole of H₂O cal. C=50.32%, H=5.2%, N=10.12%, found C=50.38%, H=4.66%, N=9.65%; ad 85.83 (sHM 300 ab CCM) FMA H (strong strong stro

A. 2-[{1-(3-Cyanobenzyl)-2-oxopyrrolidin-3-(S)-yl}-7-methoxynaphthalene-2-sulfonylamino] N-benzylacetamide.

The title compound is prepared as described in EXAMPLE 26; Part Cl-12-substituting_2-[{1-(3-cyanobenzyl)-2-oxopyrrolidin-3-(S)-yl}-7-tasny-ordenermethoxynaphthalene-2-sulfonylamino]-N-acetic acid, prepared as in

15 EXAMPLE 70. Part B, for 2-[(1-(3-cyanobenzyl)-2-oxopyrrolidin-3-(S)-yl)-7-methoxynaphthalene-2-sulfonylamino]-N-acetic acid and benzyl amine for a phenethyl amine. The title compound is obtained as a white foam: eitile of 1 h NMR (CDCI₃, 300 MHz) δ.8.42 (m, 2H), 7-79 (m, 4H), 7.60 (m, 4H), 7.21 (m, 5H), 5.53 (bs, 1H), 4.53 (m, 2H), 4.32 (m, 2H), 3.91 (s, 3H), 3.87 (m, 2H), 3.26

20 (m, 2H), 2.32 (m, 1H), 2.16 (m, 1H) encycle (1-(3-cyanol H), 2.16 (m, 1H), 2.16 (m, 1H) encycle (1-(3-cyanol H), 2-(1-(3-cyanol H), 2-(1-(3-cyanol H)))) encycle (1-(3-cyanol H), 2-(1-(3-cyanol H))) encycle (1-(3-cyanol H)) encycle (1-(3-cyanol

30 , H NMR (DMSO-d_e, 300, MHz) δ.9,27 (bs, 2H), 9.10 (bs, 2H), 8.63 (m, 1H), 8.43 (s, 1H), 7.96 (m, 2H), 7.73 (m, 2H), 7.58 (m, 4H), 7.32 (m, 1H), ε7.24 (m, 4H), 4.83 (t, 1H), 4.52 (AB, 2H), 4.30 (m, 2H), 3.89 (s, 3H), 3.85 (AB, 2H), 3.17 (m, 2H), 2.10 (m, 2H), FAB MS, [M+H] = 600. Elemental analysis calculated with 2.25 mole of H₂O, cal. C=54.14%, H=5.15%; N=9.29%; found: C=54.29%; 3.

35 H=4.73%, N=9.01%_{(for e)(file to a philogenic to the cit abovers of becaudact of section of the cities of the c}

2-[(1-[3-(Aminoiminomethyl)benzyl]-2-oxopyrrolidin-3-(S)-yl}-7-methoxynaphthalene-2-sulfonylamino]-N-(2-p-toluylethyl)acetamide trifluoroacetate.

- A. 2-[(1-(3-Cyanobenzyl)-2-oxopyrrolidin-3-(S)-yl)-7-methoxynaphthalene-2-sulfonylamino] N-(2-p-toluylethyl)acetamide.

 The title compound is prepared as described in EXAMPLE 26, Part C substituting 2-[(1-(3-cyanobenzyl)-2-oxopyrrolidin-3-(S)-yl)-7-methoxynaphthalene-2-sulfonylamino]-N-acetic acid, prepared as in
- EXAMPLE 70; Part B, for 2-[{1-(3-cyanobenzyl)-2-oxopyrrolidin-3-(S)-yl}-7-methoxynaphthalene-2-sulfonylamino]-N-acetic acid and 2-p-toluylethyl amine for phenethyl amine. The title compound is obtained as a white foam.

 ¹H NMR (CDCl₃, 300 MHz) δ 8.40 (s, 1H), 7.81 (m, 3H), 7.56 (m, 4H), 7.28 (m, 2H), 7.01 (m, 5H), 4.50 (AB, 1H), 4.41 (m, 3H), 3.91 (s, 3H), 3.76 (AB, 2H), 3.28 (m, 4H), 2.60 (m, 2H), 2.30 (m, 1H), 2.29 (s, 3H), 2.18 (m, 1H).
 - B. 2-[(1-[3-(Aminoiminomethyl)benzyl]-2-oxopyrrolidin-3-(S)-yl}-7-methoxynaphthalene-2-sulfonylamino]-(2-p-toluylethyl)acetamide trifluoroacetate.
- The title compound is prepared as described in EXAMPLE 24, Part C using 2-[{1-(3-cyanobenzyl)-2-oxopyrrolidin-3-(S)-yl}-7-methoxynaphthalene-2-sulfonylamino]-N-2-p-toluylethylacetamide as the starting material. The crude product is purified by RP-HPLC eluting in a gradient of 10% CH₃CN/H₂O (0.1% TFA) to 60% CH₃CN/H₂O (0.1% TFA) and the appropriate product fractions are lyophilized to provide the title compound as a white solid.

 H NMR (DMSO-d₈, 300 MHz) δ 9.34 (bs, 2H), 9.28 (bs, 2H), 8.42 (m, 1H), 8.21 (m, 1H), 8.05 (m, 1H), 7.95 (m, 4H), 7.77 (m, 1H), 7.68 (m, 1H), 7.57 (m, 1H), 7.31 (m, 1H), 7.05 (m, 4H), 4.79 (t, 1H), 4.50 (AB, 2H), 3.89 (s, 3H), 3.73 (AB, 2H), 3.14 (m, 4H), 2.55 (m, 2H), 2.21 (s, 3H), 2.03 (m, 2H). FAB MS,
- 30 [M+H]⁺=628.

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35 <u>trifluoroacetate.</u>

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- A. 2-[(1-(3-Cyanobenzyl)-2-oxopyrrolidin-3-(S)-yl}-7-methoxynaphthalene-2-sulfonylamino] N-(3-phenyl-propyl)acetamide. A Completion of the compound is prepared as described in EXAMPLE 26; Part Completion of the compound of the compound is prepared as described in EXAMPLE 26; Part Completion of the compound of the com
- 5 methoxynaphthalene-2-sulfonylamino]-N-acetic acid, prepared as in EXAMPLE 70, Part B, for 2-[{1-(3-cyanobenzyl)-2-oxopyrrolidin-3-(S)-yl}-7-methoxynaphthalene-2-sulfonylamino]-N-acetic acid and 3-phenyl-propyl amine for phenethyl amine. The title compound is obtained as a white foam.

 1H NMR (CDCl₃, 300 MHz) δ 8.36 (s, 1H)-7.93 (m, 1H)-7.80 (m, 3H), 7.50 (m,
- 10 3H), 7.21 (m, 5H), 7.08 (m, 2H), 4.55 (AB, 2H), 4.41 (m, 2H), 3.92 (s, 3H), 3.82 (AB, 2H), 3.93 (m, 1H), 3.85 (m, 1H), 3.09 (m, 2H), 3.48 (m, 2H), 2.39 (m, 1H), 3.6 (m, 2H), 3.60 (m, 2H), 3.80 (MHz) 3.845 (s, 3H), 7.81 (m, 3H), 7.86 (m, 4H), 7.86 (m, 4H), 7.81 (m, 3H), 7.86 (m, 4H), 7.81 (m, 3H), 7.86 (m, 4H), 7.84 (m, 3H), 7.86 (m, 4H), 7.86 (m,
- B. 2-[(1-[3-(Aminoiminomethyl)benzyl]-2-oxopyrrolidin-3-(\$)-yl)-7-70 \ HS methoxynaphthalene-2-sulfonylamino]-(3-phenyl-propyl)acetamide (Henzyl) trifluoroacetate.

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EXAMPLE 76

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A. 2-[(1-(3-Cyanobenzyl)-2-oxopyrrolidin-3-(S)-yl)-7-methoxynaphthalene-2-sulfonylamino]-N-(4-methylbenzyl)acetamide.

The title compound is prepared as described in EXAMPLE 26, Part C substituting 2-[{1-(3-cyanobenzyl)-2-oxopyrrolidin-3-(S)-yl}-7-methoxynaphthalene-2-sulfonylamino]-N-acetic acid, prepared as in EXAMPLE 70, Part B, for 2-[{1-(3-cyanobenzyl)-2-oxopyrrolidin-3-(S)-yl}-7-methoxynaphthalene-2-sulfonylamino]-N-acetic acid and 4-methylbenzyl amine for phenethyl amine. The title compound is obtained as a white foam. ¹H NMR (CDCl₃, 300 MHz) δ 8.35 (s, 1H), 8.15 (m, 1H), 7.76 (m, 2H), 7.51 (m, 5H), 7.29 (m, 3H), 6.98 (m, 2H), 4.52 (m, 3H), 4.26 (m, 2H), 3.92 (s, 3H), 3.82 (AB, 2H), 3.21 (m, 2H), 2.28 (m, 2H), 2.27 (s, 3H).

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B. 2-[{1-[3-(Aminoiminomethyl)benzyl]-2-oxopyrrolidin-3-(S)-yl}-7-methoxynaphthalene-2-sulfonylamino]-(4-methylbenzyl)acetamide trifluoroacetate.

The title compound is prepared as described in EXAMPLE 24, Part C using 2[{1-(3-cyanobenzyl)-2-oxopyrrolidin-3-(S)-yl}-7-methoxynaphthalene-2sulfonylamino]-N-4-methylbenzylacetamide as the starting material. The crude product is purified by RP-HPLC eluting in a gradient of 10% CH₃CN/H₂O (0.1% TFA) to 60% CH₃CN/H₂O (0.1% TFA) and the appropriate product fractions are lyophilized to provide the title compound as a white solid.

¹H NMR (DMSO-d₆, 300 MHz) δ 9.24 (bs, 2H), 9.10 (bs, 2H), 8.58 (m, 1H), 8.42 (s, 1H), 7.95 (m, 2H), 7.72 (m, 2H), 7.51 (m, 3H), 7.33 (dd, 1H), 7.05 (m, 4H), 4.73 (t, 1H), 4.40 (AB, 2H), 4.19 (m, 2H), 3.88 (s, 3H), 3.81 (AB, 2H), 3.14 (m, 2H), 2.24 (s, 3H), 2.06 (m, 2H). FAB MS, [M+H]*=614.

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- 25 EXAMPLE:77asi, and the shart and all the shar
- A. 2-[(1-(3-Cyanobenzyl)-2-oxopyrrolidin-3-(S)-yl)-7-methoxynaphthalene-2-sulfonylamino]-N-[2-(3-fluorophenyl)ethyl]acetamide. The title compound is prepared as described in EXAMPLE 26, Part Compound is prepared as described in EXAMPLE 26, Part Compound is prepared as described in EXAMPLE 26, Part Compound is prepared as described in EXAMPLE 26, Part Compound is prepared as described in EXAMPLE 26, Part Compound in Example 25, Part Compound in Example 26, Part Compound in Exa

ethylamine for phenethylamine. The title-compound is obtained as a white substituting 2-(11-, 3-dyanobanzyl)-3-axopyrinlidin-3-rS; yrt-7-¹H NMR (CDCl₃, 300 MHz) δ 8.38 (s, 1H), 7.98 (m, 1H), 7.89 (m, 1H), 7.78 (m, 1H), 7.54 (m), 3H), 7.25 (m, 4H), 6.87 (m, 3H), 4.62 (AB, 1H), 4.38 (m, 3H), 3.94 (s₁,3H), 3:75 (AB, 2H); 3.31: (m; 4H); 2.68 (m; 2H), 2.31: (m; 1H), 2.17 (m; 1H). amine for pheneral arane. The title compound is obtained as a white than B. 2-[(1-[3-(Aminoiminomethyl)benzyl]-2-oxopyrrollidin-3-(S)-vij-7-Filolidin-3 methoxynaphthalene-2-sülfonylaminol-N-[2-(3-fluoroohenyl)ethylläcetamide trifluoroacetate. (HS. 11), 3.2 ((1.3 H), 3.25 (m, 3.11), 3.27 (o. 3.11). 10 The title compound is prepared as described in EXAMPLE 24, Part C using 2-27 [{1-(3-cyanobenzyl)-2-oxopyrrolidin-3-(S)-yl}-7-methoxynaphthalene-2-__ sulfonylamino]-N-2-(3-fluorophenyl)ethylacetamide as the starting material. The crude product is purified by RP-HPLC eluting in a gradient of 10% with CH₃CN/H₂O (0:1% TFA) to 60% CH₃CN/H₂O (0:1% TFA) and the appropriate product fractions are lyophilized to provide the title compound as a white solid. 4.E₁(1), ¹H, NMR, (DMSO-d₆), 300 MHz) δ 9.30 (bs), 2H), 9.10 (bs; 2H), 8.42 (s), 1H)) 8.21 s 4.81; (t, 1H), 4:44 (AB; 2H), 3.99 (m; 4H), 3.95 (s, 3H); 3:60 (AB, 1H); 3:28(m). 2H), 3.13 (m, 2H), 2.72 (m; 2H), 2.04 (m; 2H). FAB MS; [M+H]*≅632; Elemental 20: A analysis cal: C=51.69%, H=4.22%, N=8.13%, found C=52.19% H=4.52%. (s. 11 ti, 7.95 (m. 2Ht. 7.72 ym, 2Ht. 7.51 (m. 2-m), 7.33 (dd. 14), 7.**368.8=N**. 677 1. 1 HJ. C., Q (AB., 2H), J.18 (m, 2H), 5.89 (s, 3H), 3.8. [AB. 2H), 6 (4 m) 25- 224 (s. 36- 205 (m. 211) FABING INSTR-614. **EXAMPLE 78** 2-[{1-[3-(Aminoiminomethyl)benzyl]-2-oxopyrrolidin-3-(S)-yl}-7-25 methoxynaphthalene-2-sulfonylaminol-N-indan-2-vlacetamide trifluoroacetate. 2-111-13-(Americianical stayI) casyI-2-oxoppe, prefer 3 (S)-VI-7 A-2-[[1-(3-Cyanobenzyl)-2-oxopyrrolidin-3-(S)-vl)-7-methoxynaphthalene-2sulfonvlamino-N-indan-2-vlacetamide. .cdveirecelate. The title compound is prepared as described in EXAMPLE 26, Part C 30 (substituting 2-[{1-(3-cyanobenzyl)-2-oxopyrrolidin-3-(S)-yl)-7-y0-8)-1 (3- A methoxynaphthalene-2-sulfonylamino]-N-acetic-acid, prepared as inverses EXAMPLE 70; Part B, for 2-[{1-(3-cyanobenzyl)-2-oxopyrrolidin-3-(S)-yl}-7-1 methoxynaphthalene-2-sulfonylaminol-N-acetic acid and 2-aminoindane for phenethylamine. The title compound is obtained as a white foam nyzoritem 35 ¹H.NMR (GDCl₃; 300 MHz) δ 8,35 (s, 1H), 8,14 (m, 1H), 7:75 (m, 3H); 7.54 (m, 4H), 7.21 (m, 5H), 4.66 (AB, 1H), 4.42 (m, 3H), 3.92 (s, 3H), 3.83 (AB, 2H), 3.35 (m, 1H), 3.18 (m, 1H), 2.94 (m, 1H), 2.75 (m, 1H), 2.37 (m, 3H).

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- B. 2-[(1-[3-(Aminoiminomethyl)benzyl]-2-oxopyrrolidin-3-(S)-yl]-7-methoxynaphthalene-2-sulfonylamino]-N-indan-2-ylacetamide trifluoroacetate.

 The title compound is prepared as described in EXAMPLE 24, Part C using 2-
- [{1-(3-cyanobenzyl)-2-oxopyrrolidin-3-(S)-yl}-7-methoxynaphthalene-2-sulfonylamino]-N-2-(3-fluorophenyl)ethylacetamide as the starting material. The crude product is purified by RP-HPLC eluting in a gradient of 10% CH₃CN/H₂O (0.1% TFA) to 60% CH₃CN/H₂O (0.1% TFA) and the appropriate product fractions are lyophilized to provide the title compound as a white solid.
- ¹H NMR (DMSO-d₆, 300 MHz) δ 9.28 (bs, 2H), 9.190 (bs, 2H), 8.40 (m, 2H), 7.95 (m, 2H), 7.70 (m, 2H), 7.54 (m, 3H), 7.33 (dd, 1H), 7.11 (m, 4H), 5.08 (t, 1H), 4.44 (AB, 2H), 4.36 (m, 1H), 3.91 (m, 2H), 3.87 (s, 3H), 3.19(m, 2H), 3.08 (m, 2H), 2.62 (m, 2H), 2.10 (m, 2H). FAB MS, [M+H]*=626. Elemental analysis calculated with 1 mole of H_2O cal. C=52.35%, H=4.51%, N=8.03%, found
- 15 C=52.40%, H=4.81%, N=8:19% has been assured to some of the control of the cont

EXAMPLE 79

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2-[(1-[3-(Aminoiminomethyl)benzyl]-2-oxopyrrolidin-3-(S)-yl}-7-methoxynaphthalene-2-sulfonylamino]-N-(2-pyridin-3-yl-ethyl)acetamide bistrifluoroacetate.

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A. 2-[{1-(3-Cyanobenzyl)-2-oxopyrrolidin-3-(S)-yl)-7-methoxynaphthalene-2-sulfonylamino]-N-(2-pyridin-3-yl-ethyl)acetamide.

The title compound is prepared as described in EXAMPLE 26, Part C substituting 2-[{1-(3-cyanobenzyl)-2-oxopyrrolidin-3-(\$)-yl}-7-

- methoxynaphthalene-2-sulfonylaminoj-N-acetic acid, prepared as in EXAMPLE 70, Part B, for 2-[{1-(3-cyanobenzyl)-2-oxopyrrollidin-3-(S)-yl}-7-methoxynaphthalene-2-sulfonylaminoj-N-acetic acid and 3-(2-ethylamino)-pyridine for phenethyl amine. The title compound is obtained as a white foam.
- 30 ¹H NMR (CDCl₃, 300 MHz) δ 8.40 (m; 3H), 7.90 (m; 1H), 7.76 (m, 2H), 7.52 (m, 3H), 7.25 (m, 4H), 4.59 (AB, 7H), 4.41 (m; 2H), 3.95 (s; 3H), 3.75 (AB, 2H), 3.30 (m; 4H), 2.68 (m; 2H); 2.21 (m; 2H). που θέθ (π, 2H), 2.68 (m; 2H); 2.21 (m; 2H). που θέθ (π, 2H), 3.30 (m; 4H), 4.68 (m; 2H); 2.21 (m; 2H). που θέθ (π, 2H), 3.30 (m; 4H), 4.68 (m; 2H); 3.31 (m; 2H). που θέθ (π, 2H), 4.68 (m; 2H); 3.31 (m; 2H). που θέθ (π, 2H), 4.68 (m; 2H); 3.31 (m; 2H). που θέθ (π, 2H), 4.68 (m; 2H); 3.31 (m; 2H). που θέθ (π, 2H), 4.68 (m; 2H); 3.31 (m; 2H). που θέθ (π, 2H), 4.68 (m; 2H); 3.31 (m; 2H), 4.68 (m; 2H); 3.31 (m; 2H), 4.68 (m; 2H); 3.31 (m; 2H), 4.68 (m; 2H); 4.68 (m; 2H)
 - B. 2-[(1-[3-(Aminoiminomethyl)benzyl]-2-oxopyrrolidin-3-(S)-yl)-7-
- 35 methoxynaphthalene-2-sulfonylaminoj-N-(2-pyridin-3-yl-ethyl)acetamide bistrifluoroacetate.

The title compound is prepared as described in EXAMPLE 24, Part C using 2-[{1-(3-cyanobenzyl)-2-oxopyrrolidin-3-(S)-yl}-7-methoxynaphthalene-2sulfonylamino]-N-2-(3-fluorophenyl)ethylacetamide as the starting material. The crude product is purified by RP-HPLC eluting in a gradient of 10% di CH₃CN/H₂O₂ (0.1% TFA) to 60% CH₃CN/H₂O₂ (0.1% TFA) and the appropriate 5 product fractions are lyophilized to provide the title compound as a white solid. ¹H NMR (DMSO-d_e, 300 MHz), δ 9.40 (bs, 2H), 9.30 (bs, 2H), 9.13 (bs, 1H), 8.39 (s, 1H), 8.27 (m, 2H), 7.95 (m, 2H), 7.69 (m, 2H), 7.54 (m, 5H), 7.30 (dd, 1H), 4.80 (t, 1H), 4.40 (AB, 2H), 3.87 (s, 4H), 3.73 (AB, 2H), 3.40 (m, 2H), 3.12 (m, 2H), 2.88 (m, 2H), 2.46 (m, 2H), 1.99 (m, 2H). FAB MS, [M+H] = 615. Elemental 10 analysis calculated with 3 mole of H2O cal. C=48.21%, H=4.72%, N=9.37%, found, C=48.28%, H=4.23%, N=8.82%, E. 111 .00 8E 1 .(HS .BA1 A1 A LA .(E1 (a), 241, 2,62 (a), 2H), (1, 1), (a), 2H), FAD MS, [a], H] =02B, Elemental sharp calculated with 1 mole of H₂O cat. C=52.35%. H=1.51%, N=20m 1 div Petaboliso 4.5-Dichlorothiophene-2-sulfonic acid {1-[3-(aminoiminomethyl)benzyli-2-oxo-15 3(S)-pyrrolidin-3-yl}amide trifluoroacetate

EXAMPLE 79 A. 4.5-Dichlorothiophene-2-sulfonic acid [1-(3-cyanobenzyl)-2-oxopyrrolidin-3-(S)-yllamide. wheth Suppryd. Whindrai nortus s. ond tringapy yorler The title compound is prepared from 3-(3-(S)-amino-2-exopyrrolidin-1-196 20 ylmethyl)benzonitrile hydrochloride as in EXAMPLE 24, Part B, substituting 4,5dichlorothiophene-2-sulfonyl chloride for 6-methoxynaphthalene-2-sulfonyl chloride. The crude product is purified by column chromatography eluting with gradient of 10% EtOAc/CH2Cl2 to 20% EtOAc/CH2Cl2 to afford the title ## 641 compound as a white foamest orgono-2-(hysosologayo 6)-1]]-2 gradituador 25 ¹H NMB (CDCI₃, 300 MHz) δ.7.52 (m, 1H), 7.42 (m, 4H), 5.78 (bs; 1H); 4.50 (AB, 2H), 3.91 (dd, 1H), 3.24 (dd, 2H), 2.61 (m, 1H), 2.10 (m, 1H) = 0.7 (3.19 //4) in althoxymaphthelene-2-suffertylaminoj-N-adecua add and 3 (2-ethylamino B. 4.5-Dichlorothiophene-2-sulfonic acid (1-[3-(aminoiminomethyl)benzyl]-2-30 ίc

30 oxo-3(S)-pyrrolidin-3-yl\amide trifluoroacetates (see 300 more H)

4,5-Dichlorothiophene-2-sulfonic acid [1-(3-cyanobenzyl)-2-oxopyrrolidin-3(S)-yl]amide is converted to the title compound as described in EXAMPLE 24,
Part C. The crude product is purified by RP-HPLC eluting with a gradient of
10% CH₃CN/H₂O₃(0.1% TFA) to 60% CH₃CN/H₂O₄(0.1% TFA) and the 115

appropriate product fractions are lyophilized to provide the title compound as a cowhite solid.

¹H NMR (DMSO-d_s, 300 MHz) δ 9.26 (bs, 2H), 9.05 (bs, 2H), 8.78 (s, 1H), 8.72 (s, 1H), 7.62 (m, 1H), 7.51 (m, 3H), 4.38 (AB, 2H), 4.19 (dd, 1H), 3.08 (m, 2H), 2.20 (m, 1H), 1.71 (m, 2H). FAB MS, [M+H]*=447. Elemental analysis calculated with 0.50 mole of H₂O cal. C=37.90%; H=3.18%, N=9.82%, found C=37.84%, H=3.20%, N=9.69%.

EXAMPLE 81

4.5-Dichlorothiophene -2-sulfonic acid 3(S)-pyrrolidin-3-yl}methylamide trifluoroacetate.

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A. 4.5-Dichlorothiophene-2-sulfonic acid [1-(3-cvanobenzyl)-2-(S)-yllmethylamide.

The title compound is prepared as described in EXAMPLE 25, Part A using 4,5dichlorothiophene-2-sulfonic acid [1-(3-cyanobenzyl)-2-oxopyrrolidin-3-(S)-

15 yl]amide, prepared as described in EXAMPLE 80, part A, and methyl iodide. The crude product is purified by column chromatography eluting with gradient of 15% EtOAc/CH2Cl2 to 25% EtOAc/CH2Cl2 to afford the title compound as a white foam.

¹H NMR (CDCl₃, 300 MHz) δ 7.58 (m, 2H), 7.40 (m, 3H), 4.82 (t, 1H), 4.41 (AB, 20 2H), 3.21 (m, 2H), 2.82 (s, 3H), 2.38 (m, 1H), 2.04 (m, 1H). ាន ស. ស. ស. ស. ២០១៩ ១៩ ១ នៅគេកា ្នាំ ១ ១ សំនៅសេ ស

B. 4.5-Dichlorothiophene-2-sulfonic acid (1-[3-(aminoiminomethyl)ben oxo-3(S)-pyrrolidin-3-yl)methylamide trifluoroacetate.

4,5-Dichlorothiophene-2-sulfonic acid [1-(3-cyanobenzyl)-2-oxopyrrolidin-3-(S)-yllmethylamide is converted to the title compound as described in EXAMPLE 24, Part C. The crude product is purified by RP-HPLC eluting with a gradient of 10% CH₃CN/H₂O (0.1% TFA) to 60% CH₃CN/H₂O (0.1% TFA) and the appropriate product fractions are lyophilized to provide the title compound as a white solid.

30 H NMH (DMSO-d_s, 300 MHz) δ 9.28 (bs, 2H), 9.15 (bs, 2H), 7.90 (s, 1H), 7.62 (m, 1H), 7:51 (m, 3H), 4:85 (t, 1H), 4:41 (AB, 1H), 3:18 (m, 2H), 2:77 (s. 3H). 2.15 (m, 1H), 1.96 (m, 1H). FAB MS, [M+H]*=461. Elemental analysis calculated with 1.25 mole of H₂O cal. C=38.17%, H=3.62%, N=9.37%, for C=38.18%, H=3.19%, N=9.06%, Title is ad in then problem (I me IV e IV.) and careen in account

After this dote, the population of thirred with 100 mm of Fig.O. The resident as no start

EXAMPLE 82

4.5-Dichlorothiophene-2-sulfonic acid (1-[3-(aminoiminomethyl)benzyll-2-oxo-3(S)-pyrrolidin-3-yl}benzylamide trifluoroacetate 2.20 (in 1H): 1.71 (m. 2H) FAB MS, [M-H] = 44 * Elargoital analysis 4.5-Dichlorothiophene-2-sulfonic acid [1-(3-cyanobenzyl)-2-oxopyrrolidin-3-(S)-vII-benzylamide. 5 1 C=27.84%, H-3.20%, N=9.69%, The title compound is prepared as described in EXAMPLE 25, Part A using 4,5dichlorothiophene-2-sulfonic acid [1-(3-cyanobenzyl)-2-oxopyrrolidin-3-(S)yl]amide, prepared as described in EXAMPLE 80, part A, and methyl iodide. The crude product is purified by column chromatography eluting with gradient of 20% EtOAc/hexanes to 40% EtOAc/hexanes to afford the title compound as 10 a white foam. 3H), 4.32 (AB, 2H), 3.03 (m, 2H), 2.18 (m, 1H), 1.88 (m, 1H) og nog eller odt dichleredriophene-2-sulforic aci 4 (1-(8-cyanobenzyl)-2-gkopyrol 15 <u>4.5-Dichlorothiophene-2-sulfonic acid {1-[3-(aminoiminomethyl)benzyl]-2- =</u> oxo-3(S)-pyrrolidin-3-yl)benzylamide trifluoroacetate. ai tous one es uno ent 4,5-Dichlorothiophene-2-sulfonic, acid [1-(3-cyanobenzyl)-2-oxopyrrolidin-3-(S)-yl]-benzylamide is converted to the title compound as described in EXAMPLE 24, Part C. The crude product is purified by RP-HPLC eluting with a 20 gradient of 10% CH_3CN/H_2O (0.1% TFA) to 60% CH_3CN/H_2O (0.1% TFA) and the appropriate product fractions are lyophilized to provide the title compound as a white solid. as a white solid.
14 NMR (DMSO-d₆, 300 MHz) 8 9.29 (bs. 2H), 9.03 (bs. 2H), 7.94 (s. 1H), 7.63 (m, 4H), 7.30 (m, 5H), 4.81 (t, 1H), 4.40 (AB, 1H), 4.20 (AB, 2H), 3.10 (m, 2H), 2.99 (m, 1H), 2.12 (m, 1H), 1.69 (m, 1H). FAB,MS, [M+H];=539, Elemental) 25 analysis calculated with 1.75 mole of H₂O cal. C=43.96%, H=3.91%, N=8.20%, found C=44.11%, H=3.49%, N=7.96%. common visit so provide the stants are is aphilized to provide the time common appropriate. tur a white solid. 30 7-Methoxy-2-napthalenesulfonic acid (1-[3-(aminoiminomethyl)benzyl]-2-oxo-3(S)-pyrrolidin-3-yl}-2-cyclopropylphenethylamide trifluoroacetate. 2.15 (m. 11:,, 1.56 (m, 1H). FAB MS, MHHP=46 2-cyclopropylphenethyl bromide. Les O.H lo elom 85.1 minut remolas To a solution of 1-phenyl-1-cyclopropane methanol (1 g, 6.8 mmol) in 35 mL of THF is added triphenylphosphine (1.7 g, 7.1 mmol) and carbon tetrabromide 35 (2.34 g, 7.1 mmol). The solution is stirred at ambient temperatures for 5 hours. After this time, the solution is diluted with 100 mL of Et₂O. The reaction mixture

is filtered and the collected solution is concentrated. The crude product is purified by column chromatography eluting with hexane to afford the title compound (1 g, 4.4 mmol) as an oil. 1 H NMR (CDCl₃, 300 MHz) δ 7.36 (m, 3H), 7.25 (m, 1H), 3.62 (s, 2H), 1.12 (m,

5 2H), 1.00 (m, 2H).

B. 7-Methoxy-2-napthalenesulfonic acid [1-(3-cyanobenzyl)-2-oxopyrrolidin-3-(S)-yl] }-2-cyclopropylphenethylamide.

The title compound is prepared as described in EXAMPLE 26, Part A using 7-methoxynaphthalene-2-sulfonic acid [1-(3-cyanobenzyl)-2-oxopyrrolidin-3-(S)-yl]amide, prepared as described in EXAMPLE 43, part A, and 2-cyclopropylphenethyl bromide. The crude product is purified by column chromatography eluting with gradient of 20% EtOAc/hexanes to 40% EtOAc/hexanes to afford the title compound as a white foam.

¹H NMR (CDCl₃, 300 MHz) δ 8.29 (s, 1H), 7.72 (m, 3H), 7.52 (m, 3H), 7.46 (m, 1H), 7.28 (m, 1H), 7.17 (m, 1H), 7.05 (m, 1H), 4.55 (AB, 1H), 4.32 (m, 2H), 3.95 (s, 3H), 3.50 (AB, 2H), 3.14 (m, 1H), 3.05 (m, 1H), 2.08 (m, 2H), 0.78 (m, 4H).

C. 7-Methoxy-2-napthalenesulfonic acid {1-[3-(aminoiminomethyl)benzyl]-20xo-3(S)-pyrrolidin-3-yl}}(2-fluorobenzyl)amide trifluoroacetate:
7-Methoxy-2-napthalenesulfonic acid [1-(3-cyanobenzyl)-2-oxopyrrolidin-3-(S)-yl]}(2-fluorobenzyl)amide is converted to the title compound as described in EXAMPLE 24, Part C. The crude product is purified by RP-HPLC eluting with a gradient of 10% CH₃CN/H₂O (0.1% TFA) to 60% CH₃CN/H₂O (0.1% TFA) and the appropriate product fractions are lyophilized to provide the title compound as a white solid.

1 H NMR (DMSO-d₆, 300 MHz) δ 9.28 (bs, 2H), 9.08 (bs, 2H), 8.26 (s, 1H), 7.78 (m, 2H), 7.62 (m, 1H), 7.53 (m, 4H), 7.44 (m, 1H), 7.30 (dd, 1H), 7.17 (m, 2H).

7.05 (m, 3H), 4.58 (t, 1H), 4.33 (AB, 2H), 3.90 (s, 3H), 3.78 (m, 1H), 3.42 (m, 3H). 1.78 (m, 1H), 0.88 (m, 1H), 0.71 (m, 3H). FAB MS; [M+H] = 583. Elemental analysis calculated with 0.5 mole of excess TFA and 0.5 mmol of H₂O cal. C=56.69%, H=4.82%, N=7.35%, found C=56.83%, H=4.94%, N=7.46%.

35 EXAMPLE 84 3 (H) 3 20 6 (HS) 30) \S.C 36 (HS) 4.08 (H

A. 4-(3-Methylphenyl)-bromobenzene, agasputan data analico ya sa rag The title compound is prepared as described in EXAMPLE 53, Part Assa substituting 3-bromotoluene for 2-bromoanisole of the crude product is purified by column chromatography eluting with hexanes to afford the title compound as a crystalline solid.

¹H NMR (CDCl₃, 300 MHz) δ.7.55 (m, 2H), 7.40 (m, 2H), 7.31 (m, 3H)), 7.18 (m, 1H), 2.39 (s, 3H).

- 10₂, B. 3'-Methylbiphenyl-4-sulfonyl chloride: chroline-0 encludid any orders the sulfonyl chloride: chroline-0 encludid any orders. The title compound is prepared as described in EXAMPLE 53, Part Birnally substituting 4-(2-methylphenyl)-bromobenzene for 4-(2-methoxyphenyl)-component bromobenzene and title compound is obtained as a white solid common to EI MS, [M]*=266 and sulface as a brown to other and mothers sent schooled.
 - m 5 LT (HB m) 98.7 (HB m) 98.
- 25 (1H), 7.21 (m, 1H), 5.32 (bs, 1H), 4.42 (AB, 2H), 3.78 (t, 3H), 3.18 (m, 2H), 2.60 (m, 1H), 2.41 (s, 3H), 2.09 (m, 1H).
- D. 3'-Methyl-biphenyl-4-sulfonic acid {1-[3-(aminoiminomethyl)benzyl]-2-oxopyrrolidin-3(S)-yl} amide trifluoroacetate.
 3'-Methyl-biphenyl-4-sulfonic acid [1-(3-cyanobenzyl)-2-oxopyrrolidin-3-(S)-yl]amide is converted to the title compound as described in EXAMPLE 24, Part C. The crude product is purified by RP-HPLC eluting with a gradient of 10% CH₃CN/H₂O (0.1% TFA) to 60% CH₃CN/H₂O (0.1% TFA) and the appropriate product fractions are lyophilized to provide the title compound as a white solid.
 35 ¹H NMR (DMSO-d₆, 300 MHz) δ 9.27 (bs, 2H), 9.09 (bs, 2H), 8.18 (d, 1H), 7.86 (m, 4H), 7.62 (m, 1H), 7.50 (m, 5H), 7.33 (m, 1H), 7.19 (m, 1H), 4.41 (AB, 2H), 4.11 (m, 1H), 3.10 (m, 2H), 2.32 (s, 3H), 2.04 (m, 1H), 1.58 (m, 1H). FAB MS,

 $[M+H]^{+}=463$. Elemental analysis calculated with 2 mmol of H_2O cal. C=52.94%, H=5.10%, N=9.15%, found C=53.04%, H=4.80%, N=8.93%.

EXAMPLE 85

5 <u>3-[{1-[3-(Aminoiminomethyl)benzyl]-2-oxopyrrolidin-3(S)-3-yl}-(7-methoxynaphthalene-2-sulfonyl)aminojacetamide trifluoroacetate.</u>

A. 3-[{1-(3-Cyanobenzyl)-2-oxopyrrolidin-3-(S)-yl}-7-methoxynaphthalene-2-sulfonylamino]- acetamide:

- The title compound is prepared as described in EXAMPLE 67, Part C substituting 3-[{1-(3-cyanobenzyl)-2-oxopyrrolidin-3-(S)-yl}-7-methoxynaphthalene-2-sulfonylamino]-N-acetic acid, for 3-[{1-(3-cyanobenzyl)-2-oxopyrrolidin-3-(S)-yl}-7-methoxynaphthalene-2-sulfonylamino]-N-propionic acid. The title compound (0.39 g; 0.77 mmol) is obtained as a white foam.
- 15 H NMR (CDCl₃, 300 MHz) δ 8.38 (s, 1H), 7.88 (m, 2H), 7.77 (m, 2H), 7.53 (m, 4H), 7.28 (m, 1H), 7.22 (m, 1H), 5.34 (bs, 1H), 4.61 (m, 2H), 4.46 (AB, 1H), 3.93 (s, 3H), 3.75 (m, 2H), 3.28 (m, 2H), 2.39 (m, 1H), 2.21 (m, 1H).
- B. 3-[{1-[3-(Aminoiminomethyl)benzyl]-2-oxopyrrolidin-3(S)-3-yl}-(7-methoxynaphthalene-2-sulfonyl)amino]acetamide trifluoroacetate.
 3-[{1-(3-Cyanobenzyl)-2-oxopyrrolidin-3-(S)-yl}-7-methoxynaphthalene-2-sulfonylamino]acetamide is converted to the title compound as described in EXAMPLE 24, Part C. The crude product is purified by RP-HPLC eluting with a gradient of 10% CH₃CN/H₂O (0.1% TFA) to 60% CH₃CN/H₂O (0.1% TFA) and the appropriate product fractions are lyophilized to provide the title compound as a white solidate and least lyophilized to provide the title compound as a white solidate and least lyophilized to provide the title compound as a white solidate and least lyophilized to provide the title compound as a white solidate and least lyophilized to provide the title compound as a white solidate and least lyophilized to provide the title compound as a white solidate and least lyophilized to provide the title compound as a white solidate and least lyophilized to provide the title compound as a white solidate and least lyophilized to provide the title compound as a white solidate and least lyophilized to provide the title compound as a white solidate and least lyophilized to provide the title compound as a white solidate and least lyophilized to provide the title compound as a white solidate and least lyophilized to provide the title compound as a white solidate and least lyophilized to provide the title compound as a white solidate and least lyophilized to provide the title compound as a white solidate product fractions are lyophilized to provide the title compound as a white solidate product fractions are lyophilized to provide the title compound as a white solidate product fractions are lyophilized to provide the title compound as a white solidate product fractions are lyophilized to provide the title compound as a white solidate product fractions are lyophilized to provide the title compound as a white solidate product fractions are lyophilized to provide the title compound as a

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3-[{1-[3-(Aminoiminomethyl)benzyl]-2-oxopyrrolidin-3(S)-3-yl)-(7-methoxynaphthalene-2-sulfonyl)amino]-2-methylacetamide trifluoroacetate.

A. 3-[(1-(3-Cyanobenzyl)-2-oxopyrrolidin-3-(S)-yl)-7-methoxynaphthalene-2-sulfonylamino]-N-2-methylacetic acid t-butyl ester.

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The title compound is prepared as described in EXAMPLE 26, Part A '-M' substituting 7-methoxynaphthalene-2-sulfonic acid [1-(3-cyanobenzyl)-2oxopyrrolidin-3-(S)-yl]amide, prepared as described in EXAMPLE 43, part A, for 6-methoxynaphthalene-2-sulfonic acid [1-(3-cyanobenzyl)-2-oxopyrrolidin-3-(S)-yl]amide and α-bromo-t-butyl propionic acid for t-butyl -bromoacetate. 5 The crude product is purified by column chromatography eluting with a sec gradient of 20% EtOAc/hexanes to 30% EtOAc/hexanes. The two compounds obtained, a higher of spot, (minor) and a lower of spot (major), are a line. A enantiomerically pure and are diastereomeric at the carbon of the acetamide. The absolute stereochemistry is not determined, but each diastereomer is 10 treated as below. The compounds are obtained as a white foams in the compounds are obtained as a white foams in the compounds. lower of spot (major product) leading to the Secution of the S ¹H NMR (CDCl₃, 300 MHz) δ 8,48 (s, 1H), 7.95 (dd, 1H), 7.86 (d, 1H), 7.78 (d, 1H), 7.58 (m, 3H), 7.44 (d, 1H), 7.19 (m, 2H), 4.51 (AB, 2H), 4.30 (t, 1H), 4.05 15 (m, 1H), 3.93 (s, 3H), 3.36 (m, 1H), 3.18 (m, 1H), 2.64 (m, 1H), 1.33 (d, 3H), 1.29 3H., 223 (m. 15), 722 (m. 1H), 534 (bs. 1H), 4.81 (m., 2H) ...46 (A.(HE, a) higher rf (minor product) of the condition of the conditi ¹H NMR (CDCl₃, 300 MHz) δ 8.60 (s, 1H), 8.21 (d, 1H), 7.83 (d, 1H), 7.79 (d, 1H), 7.51 (m, 2H), 7.24 (m, 2H), 4.82 (AB, 1H), 4.32 (m, 2H), 4.14 (m) 1H), 3.91 (s, 3H), 3.39 (m, 1H), 3.19 (m, 1H), 2.50 (m, 1H), 1.48 (s, 3H), 1.14 (s, 9H), 141 - (B-Cyunchanzy, 3) oxopynalidin-B-181-yll-7-methoxynaniritialanout B. 3-[(1-(3-Cyanobenzyl)-2-oxopyrrolidin-3-(S)-yl}-7-methoxynaphthalene-2sulfonylamino]-N-2-methylacetic acid. an anama and consequent substance of the title compound is prepared as described in EXAMPLE 26, Part B, using 3-[{1-(3-cyanobenzyl)-2-oxopyrrolidin-3-(S)-yl}-7-methoxynaphthalene-2sulfonylamino]-N-2-methylacetic acid t-butyl ester as the starting material. major product from EXAMPLE 86, Part A and Issue 1966 about 2007 PMM In FAB MS, [M+H]*=508) -0.00 (H1 /ms 83.7 (H1 /ms 93.7 (H1 / minor product from EXAMPLE 86, Part A-Little of the court of the delication FAB MS, [M+H]*=508 M BAR (H1) (m) 10.9 15 (2) 56.0 (H1) (m) 21.0 (H1)

C. 3-[(1-(3-Cyanobenzyl)-2-oxopyrrolidin-3-(S)-yl)-6-methoxynaphthalene-2sulfonylamino]-2-methylacetamide. The title compound is prepared as described in EXAMPLE 67, Part C. 35 substituting 3-[{1-(3-cyanobenzyl)-2-oxopyrrolidin-3-(S)-yl}-7methoxynaphthalene-2-sulfonylamino]-N-2-methylacetic acid for 3-[{1-(3cyanobenzyl)-2-oxopyrrolidin-3-(S)-yl)-7-methoxynaphthalene-2-

sulfonylamino]-N-propionic acid. The title compound is obtained as a white foam.

major product from EXAMPLE 86, Part B

FAB MS, [M+H]*=507.

5 minor product from EXAMPLE 86, Part B FAB MS, [M+H]*=507.

D. 3-[{1-[3-(Aminoiminomethyl)benzyl]-2-oxopyrrolidin-3(S)-3-yl]-(7-methoxynaphthalene-2-sulfonyl)amino]-2-methylacetamide trifluoroacetate.
3-[{1-(3-Cyanobenzyl)-2-oxopyrrolidin-3-(S)-yl}-7-methoxynaphthalene-2-sulfonylamino]-2-methylacetamide is converted to the title compound as described in EXAMPLE 24, Part C. The crude product is purified by RP-HPLC eluting with a gradient of 10% CH₃CN/H₂O (0.1% TFA) to 60% CH₃CN/H₂O (0.1% TFA) and the appropriate product fractions are lyophilized to provide the title compound as a white solid.
major product from EXAMPLE 86, Part C
H-NMR (DMSO-d₆, 300 MHz) δ 9.21 (bs, 2H), 8.90 (bs, 2H), 8.48 (s, 1H), 7.96 (m, 3H), 7.55 (m, 5H), 7.30 (m, 1H), 7.18 (m, 1H), 7.00 (m, 1H), 4.58 (m, 2H), 4.47 (m, 1H), 4.07 (m, 1H), 3.91 (s, 3H), 3.26 (m, 2H), 2.48 (m, 2H), 1.18 (d, 3H).

20 FAB MS, [M+H]*=524.

minor product from EXAMPLE 86, Part C

¹H NMR (DMSO-d₆, 300 MHz) δ 9.21 (bs, 2H), 8.90 (bs, 2H), 8.48 (s, 1H), 8.35 (m, 1H), 8.05 (m, 1H), 7.90 (m, 3H), 7.72 (m, 4H), 7.36 (dd, 1H), 7.20 (m, 1H), 4.71 (AB, 1H), 4.46 (m, 2H), 4.05 (m, 1H), 3.85 (s, 3H), 3.40 (m, 2H), 2.52 (m, 2H), 2.32 (m, 1H), 1.21 (d, 3H). FAB MS, [M+H]*=524.

EXAMPLE 87 (a sa brit agrico ettr ort) evip at (D,HO) cAOE (**000 of (C,HO) 7-Methoxynaphthalene-2-sulfonic acid (1-[3-(aminoiminomethyl)benzyl]-2-oxo-azetidin-3(S)-yl)amide triffuoroacetate.

A (2-Oxoazetidin-3-(S)-yl)-carbamic acid tert-butyl ester.

To a solution of Boc-L-serine (10.3 g, 50 mmol) in 75 mL of H₂O:t-BuOH (2:1) is added methoxyamine hydrochloride (23 g, 75 mmol) and 1-(3-dimethyl-aminopropyl)-3-ethylcarbodiimide hydrochloride (9.6 g, 50 mmol). After 2 hours, the solution is saturated with NaCl. The solution is extracted with EtOAc. The organic layer is dried over MgSO₄, filtered and concentrated. The

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resulting crude material is dissolved in 50 mL of pyridine and cooled to 0°C. To the solution is added methane sulfonyl chloride (7.44 g, 65 mmol). rAfter 1 hour, the solution is poured into 100 mls of cold 1 N HCI (aq.): tThe solution is diluted with EtOAc. The layers are separated and the organic layer is washed with 1 N HCl, saturated NaHCO_a and saturated NaClenThe organic layer is dried over MgSO₄, filtered and concentrated. The resulting crude material is dissolved in 50 mL of acetone and added dropwise to a solution of K2CO3 (20.7 g, 150 mmol) in 900 mL of acetone at reflux. After 1 hour, the solution is cooled to ambient temperatures. The solution is filtered through Celiters The collected organic solution is washed with 1 N HCl, saturated NaHCO at and saturated NaCl. The organic layer is dried over MgSO4: filtered and concentrated. The resulting solid is dissolved in 20 mL of THF and added dropwise to an useb ammonia solution containing sodium (2.6 go 1,13 mmol) at 78°C. After the blue color has dissipated, the solution is stirred for an additional 10 minutes. To the reaction mixture is added NH₄Cl (13.4, 250 mmol) and the solution is allowed €. to warm to ambient temperatures. The solution is filtered not he collected is m solution is concentrated. The resulting residue is recrystallized from EtOAc to give the title compound (2 g; 11 mmol) as a white solid (43 m) 32 7 (48 m) ¹H NMR (d_e-acetone, 300 MHz) δ 6.96 (bs, 1H), 6.63 (bs, 12H), 4.81 (bs, 1H), 3.40 (m, 1H), 3.21 (m, 1H), 1.40 (s, 9H). 14.60 MS. 116.44 (1.15)

B. [1-(3-Cyanobenzyl)-2-oxoazetidin-3-(S)-yl]carbamic acid tert-butyl ester. The title compound is prepared as described in EXAMPLE 23, Part B substituting (2-oxoazetidin-3-(S)-yl)-carbamic acid tert-butyl ester for a substituting (2-oxoazetidin-3-(S)-yl)-carbamic acid tert-butyl ester. The crude product is purified by column chromatography eluting with a gradient of 20% EtOAc/ CH₂Cl₂ to 30% EtOAc/CH₂Cl₂ to give the title compound as a white solid. A 3 H NMR (CDCl₃, 300 MHz) 8 7.59 (m, 2H), 7.41 (m, 2H), 5.18 (bs. 1H), 4.72 (m, 1H), 4.41 (AB, 2H), 3.41 (m, 1H), 3.23 (m, 1H), 1.41 (s, 9H).

C. 3-(3-(S)-Amino-2-oxoazetidin-1-ylmethyl)benzonitrile hydrochloride.

The title compound is prepared as described in EXAMPLE 23, Part C using [1-(3-cyanobenzyl)-2-oxoazetidin-3-(S)-yl]carbamic acid tert-butyl ester as the starting material.

Starting material.

EI MS, [M] = 187.

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D. 7-Methoxynaphthalene-2-sulfonic acid [1-(3-cyanobenzyl)-2-oxoazetidin-3-(S)-vilamide.

The title compound is prepared as in EXAMPLE 24. Part B substituting 3-(3-(S)-Amino-2-oxo-azetidin-1-ylmethyl)benzonitrile hydrochloride for 5 3-(3-(S)-amino-2-oxopyrrolidin-1-ylmethyl)benzonitrile hydrochloride and using 7-methoxynaphthalene-2-sulfonyl chloride in place of 6-1 states as methoxynaphthalene-2-sulfonyl chloride. The crude product is purified by column chromatography eluting with a gradient of 20% EtOAc/CH₂Cl₂ to 30% EtOAc/CH₂Cl₂ to give the title compound as a white solid. Explain the state of ¹H NMR (CDCl₃, 300 MHz) δ 8.31 (s, 1H), 7.89 (d, 1H), 7.78 (d, 1H), 7.66 (m,

10 2H), 7.61 (d, 3H), 7.55 (m, 2H), 7.26 (m, 1H), 5.76 (d, 1H), 5.02 (m, 1H), 3.91 (s, white solut. 3H), 3.42 (m, 1H), 3.15 (dd, 1H). 4 Control (12 Court) 400 MHz) 4 Control 8 (4 Control 2 Control 2 Control 300 MHz) 4 Co

E. 7-Methoxynaphthalene-2-sulfonic acid {1-[3-(aminoiminomethyl)benzyl]-2-15 (oxoazetidin-3(S)-yl) amide trifluoroacetate. 84 88 4 (11 m) 12.6 (116 11 7-Methoxynaphthalene-2-sulfonic acid [1-(3-cyanobenzyl)-2-oxoazetidin-3-(S)yl]amide is converted to the title compound as described in EXAMPLE 24, Part C. The crude product is purified by RP-HPLC eluting with a gradient of 10% CH₃CN/H₂O (0.1% TFA) to 60% CH₃CN/H₂O (0.1% TFA) and the appropriate 20 product fractions are lyophilized to provide the title compound as a white solid. ¹H NMR (DMSO-d_s, 300 MHz) δ 9.22 (bs, 2H), 8.90 (bs, 2H), 8.71 (d, 1H), 8.30 (s, 3H), 8.05 (d, 1H), 7.91 (d, 1H), 7.62 (m, 2H), 7.51 (m, 4H), 7.31 (dd, 1H), 4.66 (m, 1H), 4.31 (AB, 2H), 3.87 (s, 3H), 3.25 (m, 2H). FAB MS, [M+H]+=439.

are title compound is plept ad you. A (3-(5), and o-2-c covirol diness Wheelpyljbendodisks (jet objected a line Example 24 of 188, 319MAX3 25 7-Methoxynaphthalene-2-sulfonic acid (1-[3-(āminoiminomethyl)benzyll-2-oxoazetidin-3(S)-yl}benzylamide trifluoroacetate;bure enti entirethe lycetiune eleting with 70% EtCAc/nexanes aftern the title compound as a white solid A. 7-Methoxy-2-napthalenesulfonic acid [1-(3-cyanobenzyl)-2-oxoazetidin-3-

30 (S)-yl]-benzylamide: m) is 8 (H: no 87 8 (H: NA) 34 A (H: (H: NA) 68 A (H: The title compound is prepared as described in EXAMPLE 25. Part A using 7methoxynaphthalene-2-sulfonic acid [1-(3-cyanobenzyl)-2-oxoazetidin-3-(S)yl]amide, prepared as described in Example 65, part D, and benzyl bromide. The crude product is purified by column chromatography eluting with gradient of 30% EtOAc/hexanes to 40% EtOAc/hexanes to afford the title compound as охорупывіда-3-(6) vijemide is caverua to the rite compound.msoftelide in TIXAMEN ESS, Par Colline or or product is paralled by Tributh Study with a

1H NMR (CDCI₃, 300 MHz) δ 8.39 (s, 1H), 7.93 (d, 1H), 7.79 (m, 2H), 7.59 (d. 1H), 7.44 (m, 2H), 7.29 (m, 9H), 5.08 (m, 1H), 4.29 (m, 4H), 3.89 (s; 3H), 3.23 the title compound is prepared as in EXAMPLE 24. (Hty,m)s78.2; (Hty,m) 5, 3-(3)-Amino-2-oxo-sizetidin-1- /lmss-ot/)benzontrils hydrophloride for 5 B. 7-Methoxy-2-napthalenesulfonic acid (1-[3-(aminoiminomethyl)benzyll-2oxoazetidin-3(S)-vI)benzylamide trifluoroacetate. dingan (Yodiam-V grise) 7-Methoxy-2-napthalenesulfonic acid [1-(3-cyanobenzyl)-2-oxoazetidin-3-(S)yl]-benzylamide is converted to the title compound as described in EXAMPLE 24, Part C The crude product is purified by RP-HPLC eluting with a gradient of 10 __10% CH₃CN/H₂O (0.1% TFA) to 60% CH₃CN/H₂O (0.1% TFA) and the appropriate product fractions are lyophilized to provide the title compound as a white solid. 3H), 3.42 (m, 1H), 3.15 (dd, 1H), $^{1}\text{H NMR (DMSO-d}_{s}$, 300 MHz) δ 9.27 (bs, 2H), 8.99 (bs, 2H), 8.42 (s, 3H), 8.05 (d, 1H), 7.95 (d, 1H), 7.73 (d, 1H), 7.66 (d, 1H), 7.53 (m, 3H), 7.42 (m, 1H), 7.23 (m, 6H), 5.30 (m, 1H), 4.35 (AB, 2H), 4.28 (AB, 2H), 3.29 (m, 1H), 2.83 (m, 1H). T Mathony applications 2. Physical Pt. 13-cvanctopect [1+13] September 2. PAB MS, [M+H] 1,529 done to value 11 bios in forther 2. Page 11 bios. No other 2. Page 12 bios. No vijamide is sonveiled to the title compound as described in EXAMPLE 24, Fee C. The product is purified by RP4 PLO encing with a . 68.319MAX3 v 5.6.7.8-Tetrahydronaphthalene-2-sulfonic acid (1-13-(aminoiminomethyl)-20 benzyll-2-oxopyrrolidin-3(S)-yl}amide trifluoroacetate.ers equipment touborn US. 14 PART (DMSC-d, 300 MHz) & 3.02 (bs, 2H), 8.90 (1s, 2H), 8.71 (d, 1H), 8.50 A.: 5.6.7.8-Tetrahydronaphthalene-2-sulfonic acid (1-(3-cvanoben zv))-2-4.69 (m., 1H), 4.31 (AB, 2H), 3.87 (± 3H), 3.25. abima[ly-(2)-E-nibilorryqoxo The title compound is prepared from 3-(3-(S)-amino-2-oxopyrrolidin-1ylmethyl)benzonitrile hydrochloride as in EXAMPLE 24, Part B, substituting 25 5,6,7,8-tetrahydronaphthalene-2-sulfonyl chloride for 6-methoxynaphthalene-2-sulfonyl chloride. The crude product is purified by column chromatography eluting with 70% EtOAc/hexanes afford the title compound as a white solid. ¹H NMR (CDCI_{si}, 300 MHz), δ 7,60 (m, 3H), 7,48 (m, 2H), 7,45 (d, 1H), 7.22 (d, 1H), 5.20 (d, 1H), 4.46 (AB, 2H), 3.72 (m, 1H), 3.21 (m, 2H), 2.85(m, 4H), 2.60 (C) (mi.1H), 1.82 (m, 4H). MAXE at bedinged as tempera at binuncamos at the different idethoxylasphrhalene-2-sulfania apid (1 (3-byanapenzyl)-3-oxpadefidin-3-15 B. 5.6.7.8-Tetrahydronaphthalene-2-sulfonic acid (1-[3-(aminoiminomethyl)-The crude product (benzyl-2-oxo-3(S)-pyrrolidin-3-yl}amide trifluoroacetate)

35 __5,6,7,8-Tetrahydronaphthalene-2-sulfonic acid [1-(3-cyanobenzyl)-2- ... 50 }o

oxopyrrolidin-3-(S)-yl]amide is converted to the title compound as described in EXAMPLE 24, Part C. The crude product is purified by RP-HPLC eluting with a

gradient of 10% $\rm CH_3CN/H_2O$ (0.1% TFA) to 60% $\rm CH_3CN/H_2O$ (0.1% TFA) and the appropriate product fractions are lyophilized to provide the title compound as a white solid.

¹H NMR (DMSO-d₆, 300 MHz) δ 9.31 (bs, 2H), 9.10 (bs, 2H), 8.05 (bs, 1H), 7.69 (m, 1H), 7.55 (m, 5H), 7.25 (m, 1H), 4.46 (AB, 2H), 4.08 (m, 1H), 3.12 (m, 2H), 2.78 (m, 4H), 2.02 (m, 1H), 1.76 (m, 1H), 1.60 (m, 1H). FAB MS, [M+H]*=427. Elemental analysis calculated with 1.375 mmol of H₂O cal. C=50.99%, H=5.30%, N=9.91%, found C=50.98%, H=4.93%, N=9.62%.

T-Methoxy-2-napthalenesulfonic acid (1-[3-(aminoiminomethyl)benzyl]-2-oxo-3(S)-pyrrolidin-3-yl}-(2-methoxybenzyl)amide trifluoroacetate:

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A.: 7-Methoxy-2-napthalenesulfonic acid [1-(3-cyanobenzyl)-2-oxopyrrolidin-3-(S)-yl]-(2-methoxybenzyl)amide.

To a solution of 7-methoxynaphthalene-2-sulfonic acid [1-(3-cyanobenzyl)-2-oxopyrrolidin-3-(S)-yl]amide (0.12 g; 0.26 mmol), prepared as described in EXAMPLE 43, part A, in 20 mL of acetone is added K₂CO₃ (0.07 g; 0.53 mmol), 2-methoxybenzyl chloride (0.09 g, 0.28 mmol) and tetrabutylammonium iodide (0.02 g, 0.05 mmol). The resulting mixture is stirred for 48 hours, then diluted with CH₂Cl₂ and washed with saturated NaHCO₃; H₂O and saturated NaCl. The organic layer is dried over MgSO₄, filtered, and concentrated. The crude product is purified by column chromatography eluting with 3% MeOH/CH₂Cl₂ to afford the title compound as a white foam. Characteristic Legisland Column (d. 1H), 7.90 (d. 1H), 7.80 (d.

1H), 7.55 (m, 2H), 7.45 (m), 3H), 7.20 (m, 3H), 6.90 (m, 1H), 6.75 (d, 1H), 4.63 (m, 1H), 4.44 (AB, 2H), 4.43 (AB, 2H), 3.90 (s, 3H), 3.71 (s, 3H), 3.09 (m, 2H), 2.30 (m, 1H), 2.10 (m, 1H), and only odd Odd Ab all Make a bedrose of the More and M

30 31 B. 37-Methoxy-2-napthalenesulfonic acid: (11-(3-(aminoiminomethyl)) benzyl)-2-oxo-3(S)-pyrrolidin-3-yl)-(2-methoxybenzyl) amide trifluoroacetate; (10-(3-cyanobenzyl)-2-oxopyrrolidin-3-

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can (d, 1H), 7:95.(d, 1H), 7.83 (ddβ1H), 7.65 (d, 1H), 7.45 (m, 5H), 7.34 (dd, 1H),
          7.20 (m, 1H), 6.90 (m, 2H), 4.82 (m, 1H), 4.30 (AB, 2H), 3.90 (s, 3H), 3.70 (s,
 □□ × 3H), 3.15 (m, 1H); 3.05 (m, 1H), 2.206 (m, 1H), 1.70 (m, 1H), 千角的 MS. (4) (14)
  5 (1 [M+H]*=573. Elemental analysis calculated with 1.5 mmol of H<sub>2</sub>O cal.
    C=54.91%, H=4.54%, N=7.53%, found C=54.97%, H=4.63%, N=7.49%
                 Elemental analysis calculated with 1.875 mmol of H<sub>2</sub>O call C ±50 90%.
          EXAMPLE 91. SSEE AND ARREST OF CONTROL OF SECTION OF SE
          7-Methoxy-2-napthalenesulfonic acid {1-[3-(aminoiminomethyl)benzyl]-2-oxo-
          3(S)-pyrrolidin-3-vl}-(3-methoxybenzyl)amide trifluoroacetate. もっぱがちべる
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    Z-Methosy-Laraonalen-Lufton a egid (Lafat anaroj na am efigi) ti-nzvil-2-ox
          A. 7-Methoxy-2-napthalenesulfonic acid [1-(3-cyanobenzyl)-2-oxopyrrollidin-3-
          (S)-vII-(3-methoxybenzyl)amide.
   The title compound is prepared as described in EXAMPLE 68, Part A using 7-
          methoxynaphthalene-2-sulfonic acid [1-(3-cyanobenzyl)-2-oxopyrrolidin-3-(S)-21
     23 yl]amide, prepared as described in EXAMPLE 43, part A, and 3-methoxybenzyl
          bromide. The crude product is purified by column chromatography eluting with
 10 MAXE 10 Section 19 10 Ac/hexanes to afford the title compound as a white foam. I AMAXE
   - 314 NMR (CDCI<sub>3</sub>, 300 MHz) δ 8.43 (s; 1H), 7.91 (m, 2H), 7.75 (d; 1H); 7.40 (m,
20 🚅4H), 7:20 (m, 2H), 7:13 (m, 1H), 6.92 (bs, 1H), 6:82 (d, 1H), 6:70(d, 1H), 4:60
                                                                                                                                               JS
          (m, 1H), 4.45 (AB, 2H), 4.40 (AB, 2H), 3.90 (s, 3H), 3.65 (s, 3H), 3.00 (m, 2H),
       2.28 (m; 1H); 2.00 (m; 1H); but all COSpM rave bank of reyet director and
 Product is purified by column chromatography eluting with 2.5 people CH.CH.CH.
          B. 7-Methoxy-2-napthalenesulfonic acid (1-[3-(aminoiminomethyl)benzyl]-2-
      toxo-3(S)-pyrrolidin-3-vl}-(3-methoxybenzyl)amide trifluoroacerate:
       7-Methoxy-2-napthalenesulfonic acid [1-(3-cyanobenzyl)-2-oxopyrrolidin-3-
        (S)-yl]-(3-methoxybenzyl)amide is converted to the title compound as 1 m
          described in EXAMPLE 24, Part C. The crude product is purified by RP-HPLC
          eluting with a gradient of 10% CH<sub>3</sub>CN/H<sub>2</sub>O (0.1% TFA) to 60% CH<sub>3</sub>CN/H<sub>2</sub>O
         (0.1% TFA) and the appropriate product fractions are lyophilized to provide the
30
          title compound as a white solidates nearly affect the Compilean of the leave
         H NMR (DMSO-d<sub>s</sub>, 300 MHz) \delta 9.30 (bs, 2H), 9.10 (bs, 2H), 8.45 (s, 1H), 8.05
          (d, 1H), 7.95 (d, 1H), 7.85 (d, 1H), 7.67 (d, 1H), 7.52 (m, 4H), 7.40 (dd, 1H), 7.19
      (m, 1H), 6.90 (m, 2H), 6.78 (dd, 1H), 4.75 (m, 1H), 4.35 (m, 4H), 3.90 (s; 3H);
         3.62 (s, 3H), 3.12 (m, 1H), 3.00 (m, 1H), 2.19 (m, 1H), 1:78 (m, 1H). FAB MS,
   [M+H]*=573.9 Elemental analysis calculated with 0.675 mmol of H<sub>2</sub>O cal. 100
          C=56.72%, H=4.95%, N=8.02%, found C=56.72%, H=5.08%, N=7.95%.
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EXAMPLE 92

7-Methoxy-2-napthalenesulfonic acid {1-[3-(aminoiminomethyl)benzyl]-2-oxo-3(S)-pyrrolidin-3-yl}-(4-methoxybenzyl)amide trifluoroacetate.

A. 7-Methoxy-2-napthalenesulfonic acid [1-(3-cyanobenzyl)-2-oxopyrrolidin-3-(S)-yl]-(4-methoxybenzyl)amide:

The title compound is prepared as described in EXAMPLE 90, Part A using 7-methoxynaphthalene-2-sulfonic acid [1-(3-cyanobere-1)-2-oxopyrrolidin-3-(S)-10 yl]amide, prepared as described in EXAMPLE 43, pa. A, and 4-methoxybenzyl chloride. The crude product is purified by column chromatography eluting with 50% EtOAc/hexanes to afford the title compound as a white foam.

1H NMR (CDCl₃, 300 MHz) δ 8.38 (s, 1H), 7.90 (m, 2H), 7.80 (d, 1H), 7.50 (m, 1H), 7.40 (m, 2H), 7.27 (m, 1H), 6.70 (d, 2H), 6.60 (d, 2H), 4.50 (m, 1H), 4.45

15 (AB, 2H), 4.40 (AB, 2H), 3.90 (s, 3H), 3.65 (s, 3H), 3.00 (m, 2H), 2.30 (m, 1H), 2.00 (m, 1H), 2.00 (m, 1H), 2.30 (m, 2H), 3.90 (s, 3H), 3.65 (s, 3H), 3.00 (m, 2H), 2.30 (m, 2H), 2.3

- B. 7-Methőxý-2-napthalenesúlfonic acid (1-[3-(aminoiminomethyl)benzyl]-2oxo-3(S)-pyrrolidin-3-yl}-(4-methoxybenzyl)amide trifluoroacetate.
- 7-Methoxy-2-napthalenesulfonic acid [1-(3-cyānobenzyl)-2-oxopyrrolidin-3-(S)-yl]-(4-methoxybenzyl)amide is converted to the title compound as described in EXAMPLE 24, Part C. The crude product is purified by RP-HPLC eluting with a gradient of 10% CH₃CN/H₂O (0.1% TFA) to 60% CH₃CN/H₂O (0.1% TFA) and the appropriate product fractions are lyophilized to provide the 25¹¹ title compound as a white solid.

¹H NMR (DMSO-d₆, 300 MHz) δ 9.30 (bs, 2H), 9.05 (bs, 2H), 8.33 (s, 1H), 8.02 (d, 1H), 7.95 (d, 1H), 7.80 (dd, 1H), 7.70 (d, 1H), 7.55 (m, 4H), 7.35 (dd, 1H), 7.20 (d, 2H), 6.80 (d, 2H), 4.70 (m, 1H), 4.35 (AB, 2H), 3.85 (s, 3H), 3.70 (s, 3H), 3.10 (m, 1H), 2.95 (m, 1H), 2.10 (m, 1H), 1.70 (m, 1H). FAB MS, [M+H] =573.

Elemental analysis calculated with 0.5 mmol of excess TFA cal. C=54.91%, H=4.54%, N=7.53%, found C=55.04%, H=4.39%, N=7.64%.

EXAMPLE 93

7-Methoxy-2-napthalenesulfonic acid (1-[3-(aminoiminomethyl)benzyl]-2-oxo-3(S)-pyrrolidin-3-yl)(pyridin-2-ylmethyl)amide trifluoroacetate.

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yip in as, propaied as desproed in a NAMPLE 43, part A, and pylidiniggs maths bromide. The crucil promotes purified by column committee the crucil promotes and the crucil strains with them.

A. 7-Methoxy-2-napthalenesulfonic acid [1-(3-cyanobenzyl)-2-oxopyrrolidin-3-(S)-yl](pyridin-2-ylmethyl)amide, this produces a site season orbital. The title compound is prepared as described in EXAMPLE 90, Part A using 7methoxynaphthalene-2-sulfonic acid [1-(3-cyanobenzyl)-2-oxopyrrolidin-3-(S)-5 yl]amide, prepared as described in EXAMPLE 43, part A, and pyridin-2-ylmethyl chloride. The crude product is purified by column chromatography eluting with 2% MeOH/CH₂Cl₂ to afford the title compound as a white foam. H NMR (CDCl₃, 300 MHz) δ 8.45 (s, 1H), 7.91 (s, 1H), 7.80 (d, 1H), 7.50 (m, 4H), 7.20 (m, 7H), 4.70 (m, 1H), 4.50 (m, 4H), 3.91 (s, 3H), 3.10 (m, 2H), 2.25 , 10 ... (m. 1H), 2.00 (moth) a milos ya bethiya a milosag ebana editi seurotao 50% E.OAnhaxanes to offer the fille compound as a white from B. 7-Methoxy-2-napthalenesulfonic acid (1-[3-(aminoiminomethyl)benzyl)-2oxo-3(S)-pyrrolidin-3-yl}(pyridin-2-ylmethyl)amide trifluoroacetate. 7-Methoxy-2-napthalenesulfonic acid [1-(3-cyanobenzyl)-2-oxopyrrolidin-3-21 (S)-yl](pyridin-2-ylmethyl)amide is converted to the title compound as described in EXAMPLE 24, Part C. The crude product is purified by RP-HPLC eluting with a gradient of 10% CH₃CN/H₂O (0.1% TFA) to 60% CH₃CN/H₂O (0.1% TFA) and the appropriate product fractions are lyophilized to provide the title compound as a white solid. The permit representation is provided ¹H NMR (CDCl₃, 300 MHz) δ 8.50 (s, 1H), 8.15 (d, 1H), 7.90 (s, 2H), 7.80 (m, 2H), 7.70 (m, 2H), 7.45 (m, 2H), 7.25 (m, 3H), 7.15 (m, 1H), 5.10 (m, 1H), 4.55 (AB, 2H), 4.30 (AB, 2H), 3.91 (s, 3H), 3.10 (m, 1H), 2.95 (m, 1H), 2.25 (m, 1H), 1.95 (m, 1H, 1.90 (bs. 4H). FAB MS, [M+H]*=544. Elemental analysis (1) calculated with 0.35 mmol of H₂O cal. C=56.08%, H=4.66%, N=10.55%, found 25 - C=56.07%, H=5.23%, N=10.50%, OBLE & (\$1.M COD , INCRMC) BINKER. 15, 114) 7 25 (d. 144), 7, 10 (d. 144) 11.70 (d. 144), 7, 53 (m. 44)), 7 35 (d. 14 7. 27 (d., 25.4) CS. 27. 47. (et al., 26.1) (et al., 27. 7-Methoxy-2-napthalenesulfonic acid {1-[3-(aminoiminomethyl)benzyl]-2-oxo-3(S)-pyrrolldin-3-yl)(pyridin-3-ylmethyl)amide trifluoroacetate. 30 Horrison, No. 1,833%, Joune Capalitation, Nat enter A. 7-Methoxy-2-napthalenesulfonic acid [1-(3-cyanobenzyl)-2-oxopyrrolidin-3-(S)-vI]-(pvridin-3-vI-methyl)amide. EXAS PUR 93 The title compound is prepared as described in EXAMPLE 90, Part A using 7methoxynaphthalene-2-sulfonic acid [1-(3-cyanobenzyl)-2-oxopyrrolidin-3-(S)yl]amide, prepared as described in EXAMPLE 43, part A, and pyridin-3-yl-35 methyl bromide. The crude product is purified by column chromatography eluting with 5% MeOH/CH, Cl, to afford the title compound as a white foam.

¹H NMR (CDCl₃, 300 MHz) δ 8.50 (m, 1H), 8.40 (m, 1H), 7.90 (m, 3H), 7.82 (d, 1H), 7.60 (m, 1H), 7.48 (dd, 1H), 7.45 (s, 1H), 7.23 (m, 5H), 4.60 (m, 1H), 4.50 (AB, 2H), 4.45 (AB, 2H), 3.91 (s, 3H), 3.10 (m, 2H), 2.30 (m, 1H), 1.97 (m, 1H).

- B. 7-Methoxy-2-napthalenesulfonic acid {1-[3-(aminoiminomethyl)benzyl]-2-oxo-3(S)-pyrrolidin-3-yl)(pyridin-3-ylmethyl)amide trifluoroacetate.
 7-Methoxy-2-napthalenesulfonic acid [1-(3-cyanobenzyl)-2-oxopyrrolidin-3-(S)-yl](pyridin-3-ylmethyl)amide is converted to the title compound as described in EXAMPLE 24, Part C. The crude product is purified by RP-HPLC eluting with a gradient of 10% CH₃CN/H₂O (0.1% TFA) to 60% CH₃CN/H₂O (0.1% TFA) and the appropriate product fractions are lyophilized to provide the title compound as a white solid.
- ¹H NMR (DMSO-d_s 300 MHz) 8 9.30 (bs, 2H), 9.00 (bs, 2H), 8.75 (s, 1H), 8.60 (m, 1H), 8.48 (s, 1H), 8.15 (d, 1H), 8.05 (d, 1H), 8.00 (d, 1H), 7.82 (dd, 1H), 7.65 (d, 1H), 7.55 (m, 5H), 7.38 (dd, 1H), 7.20 (m, 1H), 4.95 (m, 1H), 4.50 (s, 2H), 4.40 (AB, 2H), 3.90 (s, 3H), 3.10 (m, 2H), 2.10 (m, 1H), 1.75 (m, 1H). FAB MS, [M+H]*=544.

EXAMPLE 95

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20 7-Methoxy-2-napthalenesulfonic acid (1-[3-(aminoiminomethyl)benzyl]-2-oxo-3(S)-pyrrolidin-3-yl)-(pyridin-4-yl-methyl)amide trifluoroacetate.

A. 7-Methoxy-2-napthalenesulfonic acid [1-(3-cyanobenzyl)-2-oxopyrrolidin-3-(S)-yl](pyridin-4-ylmethyl)amide.

- The title combound is prepared as described in EXAMPLE 90, Part A using 7-methoxynaphthalene-2-sulfonic acid [1-(3-cyanobenzyl)-2-oxopyrrolidin-3-(S)-yl]amide, prepared as described in EXAMPLE 43, part A, and pyridin-4-yl-methyl chloride. The crude product is purified by column chromatography eluting with 2% MeOH/CH₂Cl₂ to afford the title compound as a white foam.
- 30 ¹H NMR (CDCl₃, 300 MHz) δ 8.52 (d, 2H), 8.40 (s, 1H), 7.90 (m, 2H), 7.80 (d, 1H), 7.60 (m, 1H), 7.48 (d, 1H), 7.40 (d, 1H), 7.30 (m, 5H), 4.60 (m, 1H), 4.45 (m, 4H), 3.95 (s, 3H), 3.10 (m, 2H), 2.30 (m, 1H), 1.97 (m, 1H).
- B. 7-Methoxy-2-napthalenesulfonic acid (1-[3-(aminoiminomethyl)benzyl]-2-oxo-3(S)-pyrrolidin-4-yl) (pyridin-4-ylmethyl)amide trifluoroacetate.

 7-Methoxy-2-napthalenesulfonic acid [1-(3-cyanobenzyl)-2-oxopyrrolidin-3-(S)-yl]-(pyridin-4-yl-methyl)amide is converted to the title compound as

described in EXAMPLE 24, Part C. The crude product is purified by RP-HPLC eluting with a gradient of 10% CH₃CN/H₂O (0.1% TFA) to 60% CH₃CN/H₂O (0.1% TFA) and the appropriate product fractions are lyophilized to provide the title compound as a white solid.

 1 H NMR (DMSO-d₈, 300 MHz) δ 9.25 (bs, 2H), 9.10 (bs, 2H), 8.70 (d, 1H), 8.45 (s, 1H), 8.08 (d, 1H), 8.00 (d, 1H), 7.95 (d, 2H), 7.80 (dd, 1H), 7.65 (m, 1H), 7.53 (m, 4H), 7.40 (dd, 1H), 4.97 (m, 1H), 4.60 (AB, 2H), 4.38 (AB, 2H), 3.98 (s, 3H), 3.10 (m, 2H), 2.10 (m, 1H), 1.70 (m, 1H), FAB MS, [M+H],=544. Elemental analysis calculated with 1.275 mmol of H2O cal. C=46.26%, H=3.83%, N=7.71%, found C=46.27%, H=3.93%, N=7.61%.

The specification appropriate product fractions are 80 214MAX3 and the specific management of the spec

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title compound as a wince onlin 7-Methoxy-2-napthalenesulfonic acid {1-[3-(aminoiminomethyl)benzyl]-2-oxo-3(S)-pyrrolidin-3-yl]-(1-benzyl-1H-imidazol-2-ylmethyl)amide trifluoroacetate.

A. 7-Methoxy-2-napthalenesulfonic acid [1-(3-cyanobenzyl)-2-oxopyrrolidin-3-(S)-vI]-(1-benzyl-1H-imidazol-2-ylmethyl)amide.

The title compound is prepared as described in EXAMPLE 90, Part A using 7methoxynaphthalene-2-sulfonic acid [1-(3-cyanobenzyl)-2-oxopyrrolidin-3-(S)-

- yl]amide, prepared as described in EXAMPLE 43, part A, and 1-benzyl-1H-20 imidazol-2-ylmethyl chloride. The crude product is purified by column chromatography eluting with 2% MeOH/CH2Cl2 to afford the title compound as a white foam.
- 1H NMR (CDCl₃, 300 MHz) δ 7.88 (s, 1H), 7.77 (d, 1H), 7.65 (dd, 2H), 7.50 (s, 1H), 7.40 (m, 2H), 7.28 (m, 1H), 7.19 (m, 4H), 7.10 (d, 1H), 7.00 (dd, 2H), 6.82 (s, 1H), 5.20 (AB, 2H), 4.70 (m, 1H), 4.55 (AB, 2H), 4.20 (AB, 2H), 3.75 (s, 3H), 2.95 (m, 1H), 1.90 (m, 1H) ylichice, crepared as decirbed in EXAMP
 - B. 7-Methoxy-2-napthalenesulfonic acid {1-[3-(aminoiminomethyl)benzyl]-2oxo-3(S)-pyrrolidin-4-yl)-(1-benzyl-1H-imidazol-2-ylmethyl)amide trifluoroacetate.

7-Methoxy-2-napthalenesulfonic acid [1-(3-cyanobenzyl)-2-oxopyrrolidin-3-(S)-yl]-(1-benzyl-1H-imidazol-2-ylmethyl)amide is converted to the title compound as described in EXAMPLE 24, Part C. The crude product is purified 35 by RP-HPLC eluting with a gradient of 10% CH₃CN/H₂O (0.1% TFA) to 60% CH₃CN/H₂O (0.1% TFA) and the appropriate product fractions are lyophilized to

provide the title compound as a white solid.

¹H NMR (DMSO-d₆, 300 MHz) δ 9.30 (bs, 2H), 9.10 (ts, 2H), 8.30 (s, 1H), 8.05 (d, 1H), 8.00 (d, 1H), 7.65 (m, 14H), 5.50 (s, 2H), 5.10 (m, 1H), 4.75 (AB, 2H), 4.45 (AB, 2H), 3.95 (s, 3H), 3.10 (m, 2H), 2.05 (m, 1H), 1.80 (m, 1H). FAB MS, [M+H]⁺=623. Elemental analysis calculated with 2.5 mmol of H₂O cal. 5 C=50.11%, H=4.26%, N=8.99%, found C=50.34%, H=4.08%, N=8.60%.

EXAMPLE 97

(1-Methyl-1H-imidazol-2-yl)benzene-4-sulfonic acid (1-[3-(aminoiminomethyl)benzyl]-2-oxopyrrolidin-3(S)-yl)amide trifluoroacetate.

A. 4-(1-Methyl-1H-imidazol-2-yl)bromobenzene.

The title compound is prepared as described in EXAMPLE 53, Part A substituting 1-methyl-1H-imidazole for 2-bromoanisole. The crude product is purified by column chromatography eluting with 5% MeOH/CH₂Cl₂ to afford the title compound as a white foam:

EI MS, [M]⁺=237.

in the commence of the control of th

B. (1-Methyl-1H-imidazol-2-yl)benzene-4-sulfonyl chloride.

The title compound is prepared as described in EXAMPLE 53, Part B using 4-20 (1-methyl-1H-imidazol-2-yl)bromobenzene as the starting material.

"EI MS, [M] = 256.

"Et borg esure en la borg results has better a borg result in the starting material.

C. (1-Methyl-1H-imidazol-2-yl)benzene-4-sulfonic acid [1-(3-cyanobenzyl)-2-oxopyrrolidin-3-(S)-yl]amide.

- The title compound is prepared from 3-(3-(5)-amino-2-oxopyrrolidin-1-ylmethyl)benzonitrile hydrochloride as in EXAMPLE 24, Part B using (1-methyl-1H-imidazol-2-yl)benzene-4-sulfonyl chloride in place of 6-methoxynaphthalene-2-sulfonyl chloride. The crude product is purified by column chromatography elluting with 5% MeOH/CH₂Cl₂ to give the title compound as a white foam.

 1H NMR (CDCl₃, 300 MHz) 8 7.60 (m, 3H), 7.45 (m, 5H), 7.15 (s, 1H), 6.98 (s, 1H), 4.48 (AB, 2H), 3.95 (s, 3H), 3.75 (m, 1H), 3.20 (m, 2H), 2.60 (m, 1H), 2.00 (m, 1H).

MyRO Charsel, and concentrated. The filte compound to 63 g. d.a.mo. . ft . .

(1-Methyl-1H-imidazol-2-yl)benzene-4-sulfonic acid [1-(3-cyanobenzyl)-2-oxopyrrolidin-3-(S)-yl]amide is converted to the title compound as described in EXAMPLE 24, Part C. The crude product is purified by RP-HPLC eluting with a gradient of 10% CH₃CN/H₂O (0.1% TFA) to 60% CH₃CN/H₂O (0.1% TFA) and the appropriate product fractions are lyophilized to provide the title compound as a white solid.

¹H NMR (DMSO-d₆, 300 MHz) δ 9.30 (bs, 2H), 8.89 (bs, 2H), 8.70 (d, 1H), 7.90 (m, 1H), 7.69 (m, 4H), 7.55 (m, 5H), 4.45 (s, 2H), 4.10 (m, 1H), 3.90 (s, 3H), 3.20 (m, 2H), 2.20 (m, 1H), 1.80 (m, 1H). FAB MS, [M+H]=453. Elemental analysis calculated with 0.8 mmol of H₂O cal. C=44.93%, H=4.00%, N=12.09%, found C=45.02%, H=4.04%, N=11.79%; $\frac{1}{11}$ (N=1) (m, 1H), 1.80 (m, 1H). The molecular description of H₂O cal. C=44.93%, H=4.00%, N=12.09%, found C=45.02%, H=4.04%, N=11.79%; $\frac{1}{11}$ (m, 1H), 1.80 (m, 1H), 2.80 (m, 2H), 3.90 (s, 3H), 3.20 (m, 2H), 4.10 (m, 1H), 3.90 (s, 3H), 3.20 (m, 2H), 4.10 (m, 2H

The lifts compound is prepared as described in EXAMPLE 58, Part A set betiefing tracelled the miderale for 2-brons anisotic life and on the property of the stude of

7-Methoxy-2-napthalenesulfonic acid (1-[3-(aminoiminomethyl)benzyl]-2-oxo-3(\$)-pyrrolidin-3-yl}-(3-hydroxybenzyl)amide trifluoroacetate.nce alid 5

E! N.S. IM] 232.

A. 3-[(1.1-Dimethylethyl)dimethylsilyl]oxytoluene

To a solution of 3-hydroxytoluene (2 g, 8.5 mmol) in 20 mL of CH₂Cl₂ is added DBU (3.32 mL, 22.2 mmol) and 1.1-dimethylethyl)dimethylsilyl chloride (3.07 g, 20.34 mmol). After 1.5 hours, the solution is diluted with EtOAc. The organic solution is washed with 1 N HCl, 10% Na₂CO₃ and saturated NaCl. The organic layer is dried over MgSO₄, filtered, and concentrated. The crude product is purified by column chromatography eluting with 5% EtOAc/hexanes to afford the title compound (4.1 g, 18.5 mmol) as an oil.

25 ¹H NMR (CDCl₃, 300 MHz) δ 7.10 (dd. 1H), 6.70 (d, 1H), 6.65 (s. 1H), 6.63 (d, 1H), 2.30 (s, 3H), 1.00 (s, 9H), 0.20 (s, 6H).

B. α-Bromo-m-3-[(1,1-dimethylethyl)dimethylsilylloxytoluene
To a solution of 3-[(1,1-dimethylethyl)dimethylsilylloxytoluene. (1 g, 4.5 mmol) in
40 mL of CCl₄ is added N-bromo succinimide (0.92 g, 5.17 mmol) and benzoyl
peroxide (0.16 g, 0.45 mmol). The solution is heated to reflux. After
16 hours, the solution is diluted with EtOAc. The organic solution is washed
with 1 N HCl, 10% Na₂CO₃ and saturated NaCl. The organic layer is dried over
MgSO₄, filtered, and concentrated. The title compound (1.33 g, 4.4 mmol) is
obtained as an oil.

El MS, [M]*=301.

El MS, [M]*=301.

C. 7-Methoxy-2-napthalene sulfonic acid [1-(3-cyanobenzyl)-2-oxopyrrolidin-3-(S)-yl]-(3-hydroxybenzyl)amide.

The title compound is prepared as described in EXAMPLE 90, Part A using 7-

methoxynaphthalene-2-sulfonic acid [1-(3-cyanobenzyl)-2-oxopyrrolidin-3-(S)-yl]amide, prepared as described in EXAMPLE 43, part A, and α-bromo-m-3-[(1,1-dimethylethyl)dimethylsilyl]oxytoluene. The crude product is purified by column chromatography eluting with 45% EtOAc/hexanes to afford the title compound as a white foam. The characteristic compound as a white foam. The characteristic compound is a white foam.

10a 3H), 7.45 (m, 3H), 7.15 (m, 1H), 6.90 (m, 1H), 6.72 (dd)(1H), 5.60 (bs, 1H), 4.65 (m, 1H), 4.62 (AB, 2H), 4.30 (s, 2H), 3.90 (s, 3H), 3.05 (m, 2H), 2.30 (m, 1H), 2.00 (m, 1H).

D. 7-Methoxy-2-napthalenesulfonic acid (1-[3-(aminoiminomethyl)benzyl]-2-

15 no oxo-3(S)-pyrrolidin-3-yl}-(3-hydroxybenzyl)amide trifluoroacetate.

7-Methoxy-2-napthalenesulfonic acid [1-(3-cyanobenzyl)-2-oxopyrrolidin-3-(S)-yl]-(3-hydroxy-benzyl)amide is converted to the title compound as described in EXAMPLE 24, Part Calc The crude product is purified by RP-HPLC eluting with a gradient of 10% CH₃CN/H₂O (0.1% TFA) to 60% CH₃CN/H₂O

- ± 20, ∞ (0.1% (TFA); and the appropriate product fractions are lyophilized to provide the title compound as a white solid. a set (compound (2.0), processor)
- 1H NMR (DMSO-d₆, 300 MHz) 8,9,30 (bs, 2H), 9.00 (bs, 2H), 8.45 (s, 1H), 8.00 (c) (d, 4H), 7,95 (d, 4H), 7.85 (dd, 1H), 7.65 (dr, 1H), 7.50 (m, 4H), 7.35 (dd, 1H), 7.02 (m, 1H), 6.80 (bs, 1H), 6.65 (m, 2H), 4.75 (m, 1H), 4.37 (AB, 2H), 4.30 (AB,
 - 25 2H), 3.90 (s, 3H), 3.15 (m, 1H), 2.95 (m, 1H), 2.10 (m, 1H), 1.70 (m, 1H). FAB

 25 2H), 3.90 (s, 3H), 3.15 (m, 1H), 2.95 (m, 1H), 2.10 (m, 1H), 1.70 (m, 1H). FAB

 26 2H), 3.90 (s, 3H), 3.15 (m, 1H), 2.95 (m, 1H), 2.10 (m, 1H), 1.70 (m, 1H). FAB

 27 2H), 3.90 (s, 3H), 3.15 (m, 1H), 2.95 (m, 1H), 2.10 (m, 1H), 1.70 (m, 1H). FAB

 28 2H), 3.90 (s, 3H), 3.15 (m, 1H), 2.95 (m, 1H), 2.10 (m, 1H), 1.70 (m, 1H). FAB

 28 2H), 3.90 (s, 3H), 3.15 (m, 1H), 2.95 (m, 1H), 2.10 (m, 1H), 1.70 (m, 1H). FAB

 28 2H), 3.90 (s, 3H), 3.15 (m, 1H), 2.95 (m, 1H), 2.10 (m, 1H), 1.70 (m, 1H). FAB

 29 2H), 3.90 (s, 3H), 3.15 (m, 1H), 2.95 (m, 1H), 2.10 (m, 1H), 1.70 (m, 1H). FAB

 29 2H), 3.90 (s, 3H), 3.15 (m, 1H), 2.95 (m, 1H), 2.10 (m, 1H), 1.70 (m, 1H). FAB

 29 2H), 3.90 (s, 3H), 3.15 (m, 1H), 2.95 (m, 1H), 2.10 (m, 1H), 1.70 (m, 1H). FAB

 29 2H), 3.90 (s, 3H), 3.15 (m, 1H), 2.95 (m, 1H), 2.10 (m, 1H), 1.70 (m, 1H). FAB

 29 2H), 3.90 (s, 3H), 3.15 (m, 1H), 2.95 (m, 1H), 2.10 (m, 1H), 1.70 (m, 1H). FAB

 29 2H), 3.90 (s, 3H), 3.15 (m, 1H), 2.95 (m, 1H), 2.10 (m, 1H), 1.70 (m, 1H). FAB

 29 2H), 3.90 (s, 3H), 3.15 (m, 1H), 2.95 (m, 1H), 2.10 (m, 1H), 1.70 (m, 1H). FAB

 29 2H), 3.90 (s, 3H), 3.15 (m, 1H), 2.95 (m, 1H), 2.10 (m, 1H), 1.70 (m, 1H). FAB

 29 2H), 3.90 (s, 3H), 3.15 (m, 1H), 2.95 (m, 1H), 2.10 (m,

7-Mathoky-2-naphratenesulfonic acid (* (3-nyanobenky)-2-oxup, dollaris is. (3-yil) (3-

ens ancident touborq etringorge edi bris (AFT ett.0) Optiologica 200 accominanti della contra di bris (AFT ett.0) Optioni di

69 3 (GThe title compound is prepared as in EXAMPLE 76; Part A substituting 2-

35: in hydroxytoluene: for 3-hydroxytôlüene! The crude pròduct is purified by column (1) 00 c chromatography eluting with 10% EtOAc/hexanes to afford the title compound as anioil. (He moses to the moses the moses to the moses the moses to the moses the moses to the

NMR.(CDCI₃, 300 MHz) 8:7:14 (d,1H);7:08 (m;1H); 6.85 (m;1H), 6.75 (d, 1H), 2.20 (s, 3H), 1.00 (s, 9H), 0.20 (s;6H); (b, 2) decorate and support of the product of the control of pals . Λ hs 9, 08 HJPMAX3 ni bedinoseb as benegard of bnuoqmoo elitic of the control of the

C. 7-Methoxy-2-napthalenesulfonic acid [1-(3-cyanobenzyl)-2-oxopyrrolidin-3-

பாக dimethylethyl)dimethylsilyl]oxytoluene (0.145 g. 0.48 mmol) and K¿CO₃ (0.13 g, அதிச 0.92 mmol). The crude product is purified by column chromatography eluting வர அ20 mouth a gradient of 40% Et®Ac/hexanes to 80% EtOAc/hexanes afford the title compound (0.20 g, 0.37 mmol) as a white solid: s as in necessore elitications.

ラシ.8(日本 中 NMR(CDCI分300·MHz)δ:7.80(mβ3H);7.45《m,54H);7.20(m,51H), 7.10 (m, 75 + 55 1H), 6.95 (m; 1H); 6.70 (m;)1H), 6.50 (d; 1H); 4:90 (m, 1H); 4:40 (m, 4H), 3.90 (s, 54、06 本 /3H), 3:10 (m; 2H), 2:30 (m; 1H); 2:00 (m; 1H); 2:00 (c.8 /(H , m) 20 //

5 2H), 390 (s. 3H), 3.15 (m, 1H), 2.95 (m, 1H), 2.10 (m, 1H), 1.70 (m, 1H), 2.70 (m, 1H), 25 \(\text{c}\)

30 title compound as described in EXAMPLE 24 Part Cs. The crude product is purified by RP-HPLC eluting with a gradient of 10% CH₃CN/H₂O (0.1% TFA) to 60% CH₃CN/H₂O (0.1% TFA) and the appropriate product fractions are lyophilized to provide the title compound as a white solid. A H. NMR₂(DMSO-d₆, 300 MHz) δ 9.30 (bs, 2H), 8.95 (bs, 2H), 8.45 (s, 1H), 8.05

(dd,1H),7.95(d,4H),7.85(dd,1H),7.85(dd,1H),7.88(dd,1H),7.88(dd,2H),7.88(m,2

3H), 3.15 (m, 1H), 3.00 (m, 1H), 2.20 (m, 1H), 1.95 (m, 1H). FAB MS,

(M+H)*=559. Elemental analysis calculated with 0.5 mmol of excess TFA cal. C=53.66%, H=4.43%, N=7.53%, found C=53.94%, H=4.43%, N=7.59%.

EXAMPLE 100

7-Methoxy-2-napthalenesulfonic acid {1-[3-(aminoiminomethyl)benzyl]-2-oxo-3(S)-pyrrolidin-3-yl}(pyrazol-3-ylmethyl)amide trifluoroacetate.

A.º N-t-Butyloxýcarbonylpyrazol-3-ylmethyl bromide.

- 3-Methylpyrazole (2.04 g, 2.49 mmol) is dissolved in 25 mL acetonitrile under nitrogen, cooled in a ice bath, and treated with BOC anhydride (6.5 g, 2.98 mmol) followed by DMAP (0.303 g, 2.48 mmol). The reaction is warmed to room temperature over about two hours and diluted with ethyl acetate. The organic solution is washed with 1 N HCI, saturated NaHCO3 and saturated NaCl solution dried over Na₂SO₄, filtered, and concentrated to obtain N-t-
- butyloxycarbonyl-3-methylpyrazole (2.5 g, 13.7 mmol), El MS, [M] = 182. A portion of this material (1 g, 5.8 mmol) is dissolved in CCl₄ (20 mL); treated with N-bromosuccinimide (1.47 g, 8.26 mmol) and benzoyl peroxide (0.2 g, 0.83 mmol) and heated to reflux. After 4 hours, the solution is diluted with EtOAc washed with saturated NaHCO₃, dried over Na₂SO₄ and concentrated. The residue is chromatographed with 10 % EtOAc/hexane to yield the title compound (0.74 g, 2.85 mmol), El MS, [M] = 259/261.
 - B 7-Methoxy-2-napthalenesulfonic acid (1-[3-cyanobenzyl]-2-oxo-3(S)-pyrrolidin-3-yl}-(N-t-butyloxycarbonylpyrazol-3-ylmethyl)amide.

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- 25 A solution of 6-methoxynaphthalene-2-sulfonic acid [1-(3-cyanobenzyl)-2-coxopyrrollidin-3-(S)-yl]amide (0.30 g, 0.69 mmol) in refluxing acetone (25 mL) is treated with N-t-butyloxycarbonyl-pyrazol-3-ylmethyl bromide (0.28 g, 1.07 mmol) as described in EXAMPLE 90, Part A. Chromatographic purification (50% EtOAc/hexane to 60% EtOAc/hexane) yielded the title compound as a white solid (0.37 g, 0.6 mmol).
 - 1.60'(m, 4H), 7.30'(dd, 1H), 7.27'(s, 1H), 6.50'(d, 1H), 4.62'(m, 3H), 7.79'(d, 1H), 7.46-4-1.60'(m, 4H), 7.30'(dd, 1H), 7.27'(s, 1H), 6.50'(d, 1H), 4.62'(f, 1H), 4.47 (AB, 2H), 4.45'(ÅB, 2H), 3.94'(s, 3H), 3.24 (m, 1H), 3.14'(m, 1H), 2.26'(m, 2H), 1.63'(s, 9H). FAB MS [M+H] = 616.
 - C: 7-Methoxy-2-napthalenesulfonic acid (1-[3-(aminoiminomethyl)benzyl]-2-oxo-3(S)-pyrrolidin-3-yl)(pyrazol-3-ylmethyl)amide trifluoroacetate.

4.1.1

- 7-Methoxy-2-napthalenesulfonic acid {1-[3-cyanobenzyl]-2-oxo-3(S)-pyrrolidin-3-yl)(pyrazol-3-ylmethyl)amide(0.37 gr 0.6 mmol) is converted to the title compound as described in EXAMPLE 32, Part C. The crude product is converted to the hydrochloride salt with methanolic HCI then purified by RP-
- 5 HPLC eluting with a gradient of 5% CH₂CN/H₂O to 50% CH₃CN/H₂O; the appropriate product fractions are lyophilized to provide the title compound as a white solld (0.045 g, 0.08 mmol).

¹H NMR (DMSO-d_e, 300 MHz) δ.9.35 (bs, 2H), 9.07 (bs, 2H), 8.46 (s, 1H), 8.03

10 6.12 (s. 1H), 4.80 (t. 1H), 4.40 (two AB, 4H), 3.90 (s. 3H); 3.14 (m, 1H), 3.03 (m,

ot perf. H), 2:12 (m, 1H), 1.69 (m, 1H). FAB MS; [M+H]t=533 ; Elemental analysis rate (calculated with 1.6 mmoleof, H₂O; C=54.24%; H=5.43%; N=14.06%; refound

organic solution is washed with a reversity well-stated. %25.65.61.

ER O (S)-y)amide trifluoroacetate. om. 7 (5.5 (5.7.2.1) sbirminiscuscinori-

mmol) and heathift to reflux. After 4 hours, the substituting with End to reshed with saturated flathCo_{aldit} edited in the meshed with saturated flathCo_{aldit} edited in the meshed with saturated flathCo_{aldit} edited in the meshed with saturated flathcoald in the meshed with saturated with saturated flathcoald in the meshed with saturated with saturated with saturated flathcoald in the meshed with saturated with saturated flathcoald in the meshed with saturated with saturated flathcoald in the meshed with saturated with saturated with saturated flathcoald in the meshed with saturated with saturated flathcoald in the meshed with the meshed with saturated flathcoald in the meshed with the mes

- The title compound is prepared from 6-bromoguinoline as described in EXAMPLE 53, Part B. The solid product is collected, washed with copious amounts of hexane and ether and used without further purification.
 - B <u>/-Methory 2-naptaelenesu tonic acid (1-(3-crantenesus), 281, 2M (3</u>
- 25 B. Quinoline-6-sulfonic acid (1-[3-cyanobenzyl]-2-oxopyrrolidin-3-(S)-yl}amide 3-(3-(S)-Amino-2-oxopyrrolidin-1-ylmethyl)benzonitrile hydrochloride (0.32 g, 1.26 mmol) is suspended in 15 mL of CH₂CN. To the solution is added triethylamine (0.384 g, 3.78 mmol) followed by quinoline-6-sulfonyl chloride (0.25 g, 0.99 mmol). After stirring for 1.5 hours, the solution is diluted with
- 30 EtOAc and washed with 0.1 N aqueous HCl, water and saturated NaCl (18) solution. The organic layer is dried over Na2SO4, filtered and concentrated.

 The crude residue is purified by column chromatography (4% MeOH/CH2Cl2) to
 - I ne crude residue is purified by column chromatography (4% MeOH/CH₂Cl₂) to afford the title compound (0.146 g, 0.36 mmol), and as a solid... (1.5)

 1H NMR (CDCl₃, 300 MHz) δ 9.04 (d, 1H), 8.53 (s, 1H), 8.30 (d, 1H), 8.24 (m,
- 35 2H), 7.48-7.55 (m, 5H), 6.46 (brs, 1H), 5.29 (s, 1H), 4.45 (AB, 2H), 3.98 (t, 1H), 3.75 (m, 1H), 3.20 (m, 2H), 2.56 (m, 1H), 2.06 (m, 1H). FAB MS, [M+H]*=407.

Hereopolically remains a view and according to the

A minor component is also isolated: 2-n-Butylquinoline-6-sulfonic acid {1-[3-cyanobenzyl]-2-oxopyrrolidin-3-(S)-yl]amide (0.056 © 0.12 mmol); FAB MS, [M=H]*=463.

- C. Quinoline-6-sulfonic acid {1-[3-(aminoiminomethyl)benzyl]-2-oxopyrrolidin-3-(S)-yl}amide trifluoroacetate.
 Quinoline-6-sulfonic acid {1-[3-cyanobenzyl]-2-oxopyrrolidin-3-(S)-yl}amide (0.146 g, 0.36 mmol) is converted to the title compound as described in EXAMPLE 24, Part C. The crude product is purified by RP-HPLC eluting with a gradient of H₂O (0.1% TFA) to 100% CH₃CN/H₂O (0.1% TFA) over 35 minutes and the appropriate product fractions are lyophilized to provide the title compound as a white solid (0.050 g, 0.077 mmol) as well as unreacted starting material (0.10 g, 0.25 mmol).
 HNMR (DMSO-d₆, 300 MHz) δ 9.30 (bs, 2H), 9.05-9.10 (m, 3H), 8.61 (d, 1H), 8.58 (s, 1H), 8.40 (d, 1H), 8.16 (AB, 2H), 7.65-7.72 (m, 2H), 7.50-7.60 (m, 3H), 4.42 (AB, 2H), 4.20 (q, 1H), 3.09 (m, 2H), 2.03 (m, 1H), 1.60 (m, 1H). Ion Spray MS, [M+H]*=424. Elemental analysis calculated with 2 mole of H₂O: C=43.67%, H=3.96%, N=10.19%; found C=43.87%, H=3.63%, N=10.08%.
- 20 EXAMPLE 102

ைய த 4-Ryridin-4-ylberizene sûlfonic ácid (1-[3-(aminoiminomethyl)benzŷl]-2-ார் காட் oxopyrrolldin-3(S)-yl}amide bistrifluoroacetate. இது இது இது இது இது காட் நடித்துமை கட்டின்ற கூட்கத்த வருக்கும் தக்கும் தெரிக்கும் அவர்முக்க

Ether & with the Hills of the good with the

A. 4-(Pyridin-4-yl)-bromobenzene (long) 5 (0.0 g) F

But the state of the state of the state of

- 4-Bromopyridine hydrochloride is free based with saturated NaHCO₃ solution and extracted into methylene chloride. The organic solution is concentrated at room temperature and used immediately without further purification. A portion of the solid obtained (3 g; 19 mmol) is treated as described in EXAMPLE 53, Part A with n-butyl lithium (14.25 mL of a 1.6 M solution in THF, 22.8 mmol) and
- iodobromobenzene (5.39 g, 19 mmol). The crude product is purified by chromatography (30% EtOAc/hexanes to 60% EtOAc/hexanes) to obtain the title compound (2.59g, 11:06 mmol): 100 mmol 100 mmo
- The title compound is prepared from 4-(pyridin-4-yi)-bromobenzene as described in EXAMPLE 53, Part B, except that 2 equivalents of t-butyl lithium is

washing with copious amounts of hexane and ether. - ELMS, [M]*=253 and is used without further purification.

5. C. 4-Pyridin-4-ylbenzene sulfonic acid [1-(3-cyanobenzyl)-2-oxopyrrolidin-3-(S)-yl]amide:

The title compound is prepared from 3-(3-(S)-amino-2-oxopyrrolidin-1ylmethyl)benzonitrile hydrochloride (0.2-g, 0.79 mmol) as in EXAMPLE 24, Part
Busing 4-pyridin-4-ylbenzene sulfonyl, chloride (0.50 g, 1.98 mmol) in place of

10. 6-methoxynaphthalene-2-sulfonyl-chloride A-Theterude product is purified by obtain a white solid (0.25 g, 0.58 mmol) as they as (lomm 770.0 g 0.00) bits aline a se britishas

¹H NMR (CDCl₃, 300 MHz) δ 8.78 (m, 2H); 8.11 (d; 2H), 7.66 (m; 2H); 7.47-7.58

(m, 5H), 5.48 (s, 1H), 4.50 (AB, 2H), 3.88 (t, 1H), 3.29 (dd, 2H), 2.58 (m, 1H),

9.5*e* (s, 111), 8.40 (d, 114), 3.16 (**A.EEE≓(H+M].,€M_BAF₂(H**F**\,\m),5f,S** (_{m,}**5f**₃₄₎ 4.42 (A8, 2H), 4.20 (q, 1H), 3.09 (m, 2H), 2.03 (m, 11), 1.70 (m, 1H), 1₂₀ ⟨⟨···⟩

D. 4-Pyridin-4-ylbenzene sulfonic acid-(1-[3-(aminoiminomethyl)benzyl]-2oxopyrrolidin-3(S)-yl}amide bistrifluoroacetate. % 98 S=12 3578 87 = 0

4-Pyridin-4-ylbenzene sulfonic acid [1-(3-cyanobenzyl)-2-oxopyrrolidin-3-(S)-

- yl]amide (0.14 g, 0.32 mmol) is converted to the title compound as described in EXAMPLE, 24, Part C., The crude product is purified by RP-HPLC eluting with a gradient of 5% CH₃CN/H₂O (0.1% TFA) to 40% CH₃CN/H₂O (0.1% TFA) and the appropriate product fractions are lyophilized to provide the title compound as a white solid (0.132 g, 0.19 mmol).
- 25 ¹H NMR (DMSO:d₆, 300 MHz) δ 9.28 bs, 2H), 9.13 (bs, 2H), 8.80(bs, 1H), 8.33 (m, 1H), 7.97 (m, 5H), 7.62 (m, 1H), 7.51 (m, 3H), 4.40 (m, 2H), 4.15 (m, 1H), 3.10 (m, 2H), 2.05 (m, 1H), 1.60 (m, 1H). FAB MS, [M+H]*=450; Elemental analysis cal. C=47.86%, H=3.72%, N=10.34%, found C=47.94%, H=3.84%, N=10.40% (c. 1280); N=10.40\% (c. 1280); N=1

7-Methoxy-2-napthalenesulfonic acid (1-[3-(aminoiminomethyl)benzyl]-2-oxo-3(S)-pyrrolidin-3-yl)(thiophene-2-ylmethyl)amide trifluoroacetate;;;;;;;;

A. 7-Methoxy-2-napthalenesulfonic acid [1-(3-cyanobenzyl)-2-exopyrrolidin-3-(S)-yl](thiophene-2-ylmethyl)amide. The special of the second of

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reference about the surrect

The title compound is prepared as described in AMPLE 90, Part A using 7-methoxynaphthalene-2-sulfonic acid [1-(3-cyanobenzyl)-2-oxopyrrolidin-3-(S)-yl]amide (0.100 g, 0.23 mmol), prepared as described in EXAMPLE 43, part A, and thiophene-2-ylmethyl bromide (0.10 g, 0.56 mmol). The crude product is triturated with hexane/ether and used without further purification.

¹H NMR (CDCl₃, 300 MHz) δ 8.49 (s, 1H), 7.93 (bs 2H), 7.70 (d, 1H), 7.50 (m, 3H), 7.28 (m, 3H), 7.10 (d, 1H), 6.90 (m, 2H), 4.65 (m, 3H), 4.45 (AB, 2H), 3.93 (s, 3H), 3.09 (m, 2H), 2.28 (m, 1H), 2.04 (m, 1H). FAB MS, [M+H]⁺=532.

- B. 7-Methoxy-2-napthalenesulfonic acid (1-[3-(aminoiminomethyl)benzyl]-2-oxo-3(S)-pyrrolidin-3-yl-(thiophene-2-ylmethyl)amide trifluoroacetate.
 7-Methoxy-2-napthalenesulfonic acid [1-(3-cyanobenzyl)-2-oxopyrrolidin-3-(S)-yl-(thiophene-2-ylmethyl)amide (0.12 g; 0.23 mmol) is converted to the title compound as described in EXAMPLE 24, Part C. The crude product is purified by RP-HPLC eluting with a gradient of 10% CH₃CN/H₂O (0.1% TFA) to 100%
- by HP-HPLC eluting with a gradient of 10% CH₃CN/H₂O (0.1% TFA) to 100% CH₃CN/H₂O (0.1% TFA) and the appropriate product fractions are lyophilized to provide the title compound as a white solid (0.045 g, 0.064 mmol).

 H NMR (CD₃OD, 300 MHz) δ 8.49 (s, 1H), 7.95 (d, 1H), 7.87 (m, 2H), 7.62 (m, 4H), 7.43 (d, 1H), 7.31 (m, 2H), 6.96 (m, 1H), 6.85 (m, 1H), 4.66 (m, 4H), 3.92 (s,
- 20 3H), 3.23 (m, 2H), 2.23 (m, 1H), 2.05 (m, 1H) FAB MS, [M+H] 549. Elemental analysis calculated with 2 mmol of H₂O cal. C=51.57%, H=4.76%, N=8.02%, found C=51.70%, H=4.41%, N=7.79%.

EXAMPLE(104) THE LIPERING PROPERTY PROPERTY (AND EXAMPLE 100)

25....4-Pyridin-3-ylbenzene sulfonic acid (1-[3-(aminoiminomethyl)benzyl]-2-

80% OR, OVICA (et al. 1951 TPA) and the leat coordate product fraction the

135 programmentations. The constitution of the state of t

of the contract grass and was retrieved to the cuts and out of the residence of the grant of the contractions.

TA: 4-(Pyridin-3-yl)bromobenzener

3-Bromopyridine (6 g, 38 mmol) is treated as described in EXAMPLE 53, Part A 30. with n-butyl-lithium (28.5 mL of a 1.6 M solution in THF, 45.6 mmol) and iodobromobenzene (8.96 g) 31.7 mmol). The crude product is purified by chromatography (30% EtOAc/hexanes) to obtain the title compound (3.5 g, 14.9 mmol).

El MS, [M]+=233/235.

B. 4-Pyridin-3-ylbenzene sulfonylchloride.

 \Box c.

The title compound is prepared from 4-(pyridin-3-yl)-bromobenzene (1.75 g. ி செல்கு 'கு 7.5 mmol) as described in EXAMPLE 53; Part B except that 2 equivalents of t-A Sh butyl lithium is used to generate the starting anion. The crude solid product is a doubloid purified by washing with copious amounts of hexane followed by 100 mL of hot anhydrous CH2Cl2 and is used without further purification (1.98 g; 7.8 mmol). ль ра т "**Еl_iMS, [M]*=253.**зд) выл дн ,з) енга (ыни осо добо) ями н[™] 514), 7.28 (m, 3H), 7.10 (d. "H), 8.80 (m, 2H), 4.65 (n. 3H), 4.45 (AB, 2H), 5.15 C. 4-Pyridin-3-ylbenzene sulfonic acid [1-(3-cyanobenzŷl)-2-oxoóvrrolidin-3-(S)-yllamide. The title compound is prepared from 3-(3-(S)-amino-2-oxopyrrolidin-1-0 etylmethyl)benzonitrile hydrochloride (0.3 gt/1.2 mmol) as in EXAMPLE 24, Part -E-Mibro B. using 4-pyridin 3-ylbenzenesulfonyl chloride (0.57 g, 2.4 mmol) in place of 6methoxynaphthalene-2-sulfonyl chloride withe crude product is purified by chromatography: (2.5% MeOH/CH2Cl2 to 5% MeOH/CH2Cl2) to obtain a white 5. solid (0.08,9,0.18 mmol) or to tracking a diw g. क्यां जापनामा प्र 1H NMR (CD₃OD, 300 MHz) δ 8,85 (bs, 2H), 8:57 (bs, 2H)), 8:16 (d.1H), 7.94 (AB, 4H), 7.46-7.65 (m, 5H), 4.44 (AB, 2H), 4:23 (t, 1H), 3:20 (m, 2H), 2.33 (m, HONA (CD, CD, 300 W/2) 68 49 (S, 4H), 7 28 (L(H), m) 78, A, (H), (H), (H) 와 전 (전 기타) 도요기(m, 2대), 6.36 (m) 기타). 8.88 (m, 기타) 속 66 (m 과타) 강조기 20 D. 4-Pyridin-3-ylbenzenersulfonic acid (1-[3-(aminoiminomethyl)benzyl]-2-2006 B- oxopyrrolidin-3(S)-yl)amide bistrifluoroacetately bendicited also dense 4-Pyridin-3-ylbenzene sulfonic acid [1-(3-cyanobenzyl)-2-oxopyrrolidin-3-(S)yl]amide (0.08 g, 0.18 mmol) is converted to 4-pyridin-3-ylbenzene-4-sulfonic acid {1-[3-(aminoiminomethyl)benzyl]-2-oxopyrrolidin-3(S)-yl}-amide 25 bistrifluoroacetate as described in EXAMPLE 24, Part Cy-The crude product is purified by RP-HPLC eluting with a gradient of 10% CH3CN/H2O(0:1% TFA) to 60% CH₃CN/H₂O (0.1% TFA) and the appropriate product fractions are lyophilized to provide the title compound as a white solid (0.016;g, 0.024 2-Bromopyridine (6 g. 35 maps) is treated as obsorbed to EXX**(lomm**.) 30 ..., ¹H, NMR (DMSO-d₆, 300 MHz) δ 9.27 (bs, 2H), 9.05 (bs; 2H); 8.23 (m; 2H), 7.93 ... (m, 4H), 7.62 (m, 2H), 7.51 (m, 3H), 4.40 (m, 2H), 4.15 (m, 1H), 3:10 (m, 2H), շ......2.05.(m, 1H),-1.60-(m,-1H). "FAB MS, [M+H]*≘450: Ի γ...α թթեթագրել ե

EXAMPLE 105

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N-Methylpyrid-4-ylphenyl-4-sulfonic acid (1-[3-(aminoiminomethyl)benzyl]-2-35 oxopyrrolidin-3(S)-yl}amide trifluoroacetate: helitaet(y-6-minuv2-b ...\$

17 1 A 1911 1 KE

Pyrid-4-ylbenzene sulfonic acid {1-[3-cyanobenzyl]-2-oxopyrrolidin-3(S)-yl} amide (0.25 g, 0.58 mmol), prepared as described in EXAMPLE 80, Part C is converted to the title compound as described in EXAMPLE 32, Part C. The crude product is purified by RP-HPLC eluting with a gradient of 10%

5 CH₃CN/H₂O (0.1% TFA) to 60% CH₃CN/H₂O (0.1% TFA) and the appropriate product fractions are lyophilized to provide the title compound as a yellow solid (0.055, 0.08 mmol).

1H NMR (CD₃OD, 300 MHz) δ 8.42,8.98 (AB, 4H), 8.16 (s, 4H) 7.56-7.73 (m,

3H), 7.59 (s,:1H), 4.50 (AB, 2H), 4.43 (s, 3H), 4.27 (t, 1H), 3.26 (m, 2H), 2.33 (m,

APT Pros (APT Print) CHRID, HO 2000 CH (APT Your CogRess 2) いっぱい いた、EXAMPLE:106以のようではない。このできてなけるによるによっぱっぱっぱん

2-Methoxyquinoline-7-sulfonic acid (1-[3-(aminoiminomethyl)benzyl)-2oxopyrrolidin-3-(S)-yl)amide trifluoroacetate.

2. 15 € MA; 8.8 № (Horogonia Institute of the m) 68.0 08 √ (Attribute of the model of the mo

7-Bromo-2-methoxyquinoline (1.75 g; 7.5 mmol) is treated as described in EXAMPLE 53, Part B. The crude solid product is collected, washed with hexane and used without further purification (0.66 g, 2.6 mmol).

20 EI MS, [M]+=257.

B. 2-Methoxyquinoline-7-sulfonic acid [1-[3-cyañobenzyl]-2-oxopyrrolidin-3-

The title compound is prepared from 3-(3-(S)-amino-2-oxopyrrolidin-1-

- ylmethyl)benzonitrile hydrochloride (0.305, 4:2 mmol) as in EXAMPLE 24, Part B using 2-methoxyquiholine-7-sulfonyl chloride (0.30 g, 1.16 mmol) in place of 6-methoxynaphthalene-2-sulfonyl chloride. Acid (1-[3-cyanobenzyl]-2-oxopyrrolidin-3-(S)-yl]amide is obtained as a solid (1-[3-cyanobenzyl]-2-oxopyrrolidin-3-(S)-yl]amide is obtained as a solid (0.27 g-0.62 mmol) upon chromatography (CH₂Cl₂ to 3% MeOH/CH₂Cl₂).
 - 1H NMR (CDCl₃, 300 MHz) δ 8.43 (m, 2H), 8.03 (d, 2H), 7.80-7.91 (m, 2H), 7.58 (d, 1H), 7.43 (m, 3H), 7.06 (d, 1H), 5.43 (s, 1H), 4.43 (s, 2H), 4.08 (s, 3H), 3.80 (t, 1H), 3.20 (dd, 2H), 2.62 (m, 1H), 2.10 (m, 1H). El MS, [M]⁺=436.

CP:-Methoxyguinoline-7-sulfonic acid (1-[3-cyanobehzyi]-2-oxopyrirolidin-3-(S)-15 35 (Pan description of description of the EXAMPLE S3, Pan B. This individual of the major of the majo

yl)amide (0.15 g, 0.35 mmol) is converted to the title compound (0.157 g, 0.35

mmol) as described in EXAMPLE 90; Part A except that acetone is replaced at Construction anhydrous DMF (4 mL) and a catalytic amount of tert-butyl ammonium genvaried to the title compound as described in EX babbs algebibol EI MS. [M] = 450. Attive entitle SuffH-9A yet be in a 1 2 tout one oburo CHICHARD (0.1% TEA) to 66% CHICHARD (0.1% TEA) and the approduction 1581-2- Wolfer D. 2-Methoxyquinoline-7-sulfonic acid {1-[3-(aminoiminomethyl)benzyl]-2oxopyrrolidin-3-(S)-yl}amide trifluoroacetate. Mos in 60 0 (280.1) 2-Methoxy-quinoline-7-sulfonic acid {1-[3-cyanobenzyl]-2-oxopýrrolidin-3-(S)-TO BE 3 174 yll methylamide is converted to the title compound as described in EXAMPLE 24, Part C. The crude product is purified by RP-HRLC eluting with a gradient of 10% $\mathrm{CH_3CN/H_2O}$ (0.1% TFA) to 100% $\mathrm{CH_3CN/H_2O}$ (0.1% TFA) and the appropriate product fractions are lyophilized to provide the title compound as a 2-Liwhite solid (0.038, 0.065 mmol). bios product - aniophysycotte 4-2 ¹H NMR (CD₃OD, 300 MHz), δ 8.35 (s, 1H), 8.25 (d, 1H), 7.98 (d, 3H), 7.84 (dd, 1H), 7.69 (m, 1H), 7.50-7.68 (m, 3H), 7.10 (s,1H), 5.0 (t, 1H), 4.53 (AB, 2H), 4.08 15 (s, 3H), 3.30 (m, 2H), 2.80 (s, 3H), 2.15 (m, 1H), 1.93 (m, 1H) FAB MS, is ber [M+H]*=468, Elemental analysis calculated with 1.5 mmol of TFA and 0.5 mmol dicof, H₂O: C=48.2%, H=4.28%, N=10.81%, found C=48.16%, H=4.37%, N=10,67%, 3.8 to 38.0) roll within plant to the base one energy 20 O M3, 1M1 2557. 951 **EXAMPLE 107** 8-n broad-(6-Methoxypyridin-2-yl)benzene-4-sulfonic acid (1-[3- paterios] 8 (aminoiminomethyl)benzyl]-2-oxopyrrolidin-3(S)-yl]amide bistrifluoroacetate. The tith comprising is propried from 3-13-(\$)-amino-2-expayreligin-1-25 - Ar. 4-(6-Methoxypyridin-2-vi)bromobenzenezyd elizinesi ed(lydfemly 35 ro Hobita n2-Bromo-6-methoxypyridine (3.g., 17, mmol) is treated as described in EXAMPLE 53, Part A with n-butyl lithium (10.6 mL of a 1.6 M solution in THF. 17 mmol) and lodobromobenzene (4,8 g, 17 mmol). The crude product is purified by chromatography (5% EtOAc/hexanes) to obtain the title compound "HIMMEL (CUCILL 200 MHz) & 8.41 Pa. 2H, 8 00 (d. 2H(lomm 9.7) 21 21 21 (8) 38 1 70 6 El MS, [M]: =263/265. 700 (a) 30 (a) 10 (b) 30 (x (80 (a) 84 x (H t b) it in the state of B. 4-(6-Methoxypyridin-2-yl)benzene sulfonyl chloride. The title compound is prepared from 4-(pyridin-4-yl)-bromobenzene (1.92 g. 7.5 mmol) as described in EXAMPLE 53, Part B. The crude product is purified

- (fr. in by chromatography to give 4-(6 methoxypyridin-2-yl)benzene sulfonyl chloride.

C. 4-(6-Methoxypyridin-2-yl)benzene-4-sulfonic acid [1-(3-cyanobenzyl)-2-oxopyrrolidin-3-(S)-yl]amide.

The title compound is prepared from 3-(3-(S)-amino-2-oxopyrrolidin-1-

- ylmethyl)benzonitrile hydrochloride (0.59 g, 2.3 mmol) as in EXAMPLE 24, Part B using 4-(6-methoxypyridin-2-yl)benzene sulfonyl chloride (0.63 g, 2.2 mmol) in place of 6-methoxynaphthalene-2-sulfonyl chloride. The crude product (1.1 g, 2.4 mmol) is used without further purification.

 1H NMR (CDCl₃, 300 MHz) δ 8.20 (d, 2H), 7.98 (d, 2H), 7.66 (t, 1H), 7.57 (m,

- 4-(6-Methoxypyridin-2-yl)benzene-4-sulfonic acid [1-(3-cŷanobenzỳl)-2-coxopyrrolidin-3-(S)-yl]amide (0.26g, 0.57 mmol) is converted to the title compound as described in EXAMPLE 24, Part C. The crude product is purified by RP-HPLC eluting with a gradient of 10% CH₃CN/H₂O (0.1% TFA) to 100% CH₃CN/H₂O (0.1% TFA) and the appropriate product fractions are lyophilized to

52H);,2.29 (m,√H); 1.78 (m; 1H)./ FAB MS\$[M∓H]*=480:-ก็ไม่เอาจุดุติด ต ระบาง , / กา เอยของอาจะระบาง ธนากี เปิด มีเดิม 2.4. กินส์ เลยของอย่าง a bound mos

- 25 \ 'EXAMPLE (108, Fire O, HO & C. The mellong is new and the OLIFER THE VOICE TO BE A seried of the C. Chloropyridin-2-yloxy) benzene-4-sulfonic acid (1-13-2, HO) (aminoiminomethyl) benzylf-2-oxopyrrolidin-3(S)-yl) amide (fiffuoroacetate, a number of the Cost and Cost acid (1-13-2, HM) the
 - at A.S4-(3-Chloropyridin-2-vloxy)bromoberizene: (i 17 m) 88.7 (HS m)
 - Bromopheñol (3:74 g,\22 mmol) is stirred with 50% sodium hydroxide solution (16 mL) for about 1 hour then treated with hexadecyltributylphosphonium bromide (3.25 g; 6.4 mmol), 2.3-dichloro-pyridine (3.2 g, 21.6 mmol) and toluene (15 mL). The mixture is heated to 100°C for 18 hours, cooled and diluted with ethyl acetate and water. The organic layer is separated, washed with dilute NaOH and saturated NaOF dried (MgSO) and concentrated. Flash
 - with dilute NaOH and saturated NaCladried (MgSO₄) and concentrated. Flash suchromatography (5% EtÖAc/héxàñés) yielded the title compound (4.4 g, 15 mmol).

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EI MS, [M]+= 285.
      Q. 4-16-Methoxyoyard n-2 youanxens A surfroid acr. 1 (3-cyanobenzyl- --
                     B. 4-(3-Chloropyridin-2-yloxy)benzene sulfonyl-chlorideptlomycoxc
                1-14-(3-Chloropyridin-2-yloxy)bromobenzene (2 g, 7.03 mmol) is converted to the
ா அத்த துetitle compound as described in EXAMPLE 53, Part Bi The crude product? a
 Homes & gummy solidatis purified by chromatography (CH,Cl,) to Vield 4-(3-5
  * 11 - ho chloropyridin-2-yloxy)benzene sulfonyl chloride (0.76 g. 2.5 mmol).
                    EI MS, [M]+=303.
                                                         in 2.4 nmoly is used without further purification
       'H NMR (CDCI<sub>a</sub>, 300 MHz) 8 8.20 (d. 1H), 7.95 (d. 2H), 7 66 (t. 1H), 7.37 (m)
    10, E 4-(3-Chloropyridin-2-yloxy)benzene sulfonic acid [1-(3-cvanobenzyl)-2-
                    3.78 (t, 1H), 3.21 (m, 2H), 2.61 (m, 1H), 4.21 (m, 2H), 2.61 (m, 1H), 4.21 (m, 2H), 4.
                    The title compound is prepared from 3-(3-(S)-amino-2-oxopyrrolidin-1-
                    ylmethyl)benzonitrile hydrochloride as in EXAMPLE 24 Part B using 4-(3-
    entities chloropyridin-2-yloxy)benzene sulfonylchloride in placecof 6-onims)
          15c.//methoxynaphthalene-2-sulfonyl/chloride>d(ly-S-nihiryqyxodiaM-8)-5
             - 6/11/H,NMR.(CDCI<sub>3</sub>, 300 MHz),δ.8.07 (d.1H), 7:96 (d, 2H), 7:82 (d, 1H) × 7.58 (m.
 i. Minua e (1H), 7,46 (m, 3H); 7,32 (d, 2H), 7,07 (dd, 1H), 5,35 (s, 1H), 4,46 (s, 2H), 3,78 (t,
     argon of 1H), 3.21 (dd, 2H), 2.58 (m; 1H), 2:08 (m. 1H) iw poiture 0.14H-44 vd
  CHICNING OF 191 TEAH and the appropriate product fractions are lysurfaced to
                   D. 4-(3-Chloropyridin-2-vloxy)benzene-4-sulfonic acid (1-132 spivong
   1) ST.T. ((aminoiminomethyl)benzyl]-2-oxopyrrolidin-3(S)-vilamide trifluoroacetate.
  4-(3-Chloropyridin-2-yloxy)benzene sulfonic acid-[1-(3-cyanobenzyl)-2-
                   oxopyrrolidin-3-(S)-yl]amide:(0:47 g; 0.97 mmol) is converted to the title
                   compound as described in EXAMPLE 24, Part C. The crude product is purified
         25
                   by RP-HPLC eluting with a gradient of 15% CH<sub>3</sub>CN/H<sub>2</sub>O<sub>2</sub>(0.1%:TFA) to 70%
                   CH₂CN/H₂O (0.1%:TFA) and the appropriate product fractions are lyophilized to
          provide the title compound as a white solid (0.4 g, 0.64 mmol) ion must
                    ^{1}H NMR (DMSO-d<sub>s</sub>, 300 MHz) \delta 9.26 (bs, 2H), 9.15 (bs, 2H), 8.16 (d, 1H), 8.05
                   (m, 2H), 7.85 (m, 2H), 7.62 (m, 1H), 7.51 (m, 3H), 7.30 (m, 2H), 7.22 (m, 1H),
   30, 4.41 (AB, 2H), 4.13 (m, 1H), 3.08 (m, 2H), 2.04 (m, 1H), 1.60 (m, 1H). 3FAB MS,
           [M+H] =500. Elemental analysis calculated with 0.5 mmol of H<sub>2</sub>O: C=48.20%,
           H=3.88%; N=11.24%, found, C=48.23%, H=3.56%, N=10.97%; instance
          rowene (1) mL). The mixture is heated to 100°C for 18 hours, milled and
    tradesw EXAMPLE 109 well almost edit increw bins stated in the die behalb
      - 35 ..., 4-(N-Oxidopyridin-3-yl)benzene-4-sulfonic acid (1-[3-0]sit abilib refiv.
                  .(aminoiminomethyl)benzyl]-2-oxopyrrolidin-3(S)-yl) amide trifiuoroacetate.
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1.0100

A. 4-(N-Oxidopyridin-3-yl)benzene sulfonic acid [1-(3-cvanobenzyl)-2oxopyrrolidin-3-(S)-yllamide

4-Pyridin-3-ylbenzene sulfonic acid [1-(3-cyanobenzyl)-2-oxopyrrolidin-3-(S)vilamide (0.125 g. 0.29 mmol) is treated with m-chloroperbenzoic acid (0.55 g.

- 5 3.2 mmol) in chloroform (4 mL) for 20 hours. The reaction is diluted with methylene chloride, washed with saturated NaHCO3 and saturated NaCl, dried (Na₂SO₄) and concentrated to yield 4-(N-oxypyridin-3-yl)benzene sulfonic acid {1-[3-(aminoiminomethyl)benzyl]-2-oxopyrrolidin-3(S)-yl} amide (0.12 g, 0.27 mmol). The crude product is used without further purification.
- 10 ¹H NMR (CDCI₃, 300 MHz) δ 8.50 (bs, 1H), 8.28 (d, 1H), 8.06 (d, 2H), 7.68 (d, 2H), 7.36-7.60 (m, 5H), 6.00 (m, 1H), 4.46 (AB, 2H), 3.90 (m, 1H), 3.25 (m, 2H), 2.60 (m, 1H), 2.08 (m, 1H). FAB MS, [M+H]+=449.

B. 4-(N-Oxidopyridin-3-yl)benzene-4-sulfonic acid [1-[3-

- (aminoiminomethyl)benzyl]-2-oxopyrrolidin-3(S)-yl) amide trifluoroacetate. 15 4-(N-Oxidopyridin-3-yl)benzene-4-sulfonic acid [1-(3-cyanobenzyl)-2oxopyrrolidin-3-(S)-yl]amide (0.12 g, 0.27 mmol) is converted to the title compound as described in EXAMPLE 24, Part C. The crude product is purified by RP-HPLC eluting with a gradient of 10% CH₂CN/H₂O (0.1% TFA) to 60%
- 20 CH₂CN/H₂O (0.1% TFA) and the appropriate product fractions are lyophilized to provide the title compound as a white solid (0.045 g, 0.07 mmol). ¹H NMR (DMSO-d_s, 300 MHz) δ 9.26 (bs, 2H), 9.00 (bs, 2H), 8.62 (m, 1H), 8.38 (m, 2H), 7.94 (m, 4H), 7.65 (m, 2H), 7.50 (m, 4H), 4.40 (AB, 2H), 4.13 (m, 1H), 3.10 (m. 2H), 2.05 (m. 1H), 1.59 (m. 1H). FAB MS, [M+H] = 466. 6 15 3 - 17 20 C V=13 . 報意· 5

Section 5 Health 1997 (1994)

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EXAMPLE 110

4-Phenoxybenzene-4-sulfonic acid {1-[3-(aminoiminomethyl)benzyl]-2oxopyrrolidin-3(S)-vl} amide trifluoroacetate. Active A control of the property of the second of the seco

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A. 4-Phenoxybenzene sulfonyl chloride. 30

4-(Phenoxy)bromobenzene (6 g, 24 mmol) is converted to the title compound as described in EXAMPLE 53. Part B. The final suspension is concentrated and the residue is purified by chromatography (2% ether/hexane) to yield 4phenoxybenzene sulfohyl chloride (3.92 g, 14.6 mmol): 5 35 FEI'MS?[MI*=468.96d nexterel-1] bloe block te-9-viralen dut syvaatom

V. 49 Har (O 1044 Build), prejound as described AX (MP.E 42) on A

30

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B. 4-Phenoxybenzene sulfonic acid [1-(3-cyanobenzyl)-2-oxopyrrolidin-3-(S)-yllamide.

The title compound is prepared from 3-(3-(S)-amino-2-oxopyrrolidin-1-ylmethyl) benzonitrile hydrochloride (0.35 g. 1.39 mmol) as in EXAMPLE 24,

5 Part B using 4-phenoxybenzene-4-sulfonyl chloride (0.38 g. 1.41 mmol) in place of 6-methoxynaphthalene-2-sulfonyl chloride. Standard work-up and chromatography gave 4-phenoxybenzene sulfonic acid [1-(3-cyanobenzyl)-2-oxopyrrolidin-3-(S)-yl]amide (0.37 g. 0.83 mmol): The crude product is triturated with hexane/ether and used without further purification and 10 γ (H. NMR (CDCI), 300 MHz) δ 7.86 (d. 2H), (7.63 (d. 1H), 7.40-7.50 (m. 5H), 7.22 (d. 1H), 7.09 (t. 4H) 5.24 (s. 1H), 4.47 (AB, 2H), 3.77 (to 1H), ε3:20 (dd. 2H), 2.58 (m. 1H), 2.09 (m. 1H), EAB MS, [M+H] = 447 (m. 80.9 (H. m.) 08 9

C. 4-Phenoxybenzene sulfonic acid {1-[3-(aminoiminomethyl)benzyl]-2-

20 Oxopyrrolidin-3(S)-yl)amide trifluoroacetate and demonimismine)

4. Phenoxybenzene sulfonic acid [1-(3-cyanobenzyl)-2-oxopyrrolidin-3-(S)-yl]amide (0,37,g, 0.83 mmol) is converted to the title compound as described in EXAMPLE 24. Part C. The crude product is purified by RP-HPLC eluting with a gradient of 25% CH₂CN/H₂O (0,1% TEA) to 100% CH₃CN and the appropriate product fractions are lyophilized to provide the title compound as a white solid (0.25 g, 0.426 mmol) of the serious as boundary and the solid (0.25 g, 0.426 mmol) of the serious as boundary and the solid (0.25 g, 0.426 mmol) of the serious as boundary and the solid (0.25 g, 0.426 mmol) of the serious as boundary and the solid (0.25 g, 0.426 mmol) of the serious as boundary and the solid (0.25 g, 0.426 mmol) of the serious as boundary and the solid (0.25 g, 0.426 mmol) of the serious as boundary and the solid (0.25 g, 0.426 mmol) of the serious as boundary and the solid (0.25 g, 0.426 mmol) of the serious as boundary as a white solid (0.25 g, 0.426 mmol) of the serious as boundary as a serious and the serious as a serious as a

EXAMPLE 111

Selection and (1-[3-(aminoiminomethyl)benzyl]-2-oxo-3(S)-pyrrolidin-3-yl}(thiophene-3-ylmethyl)amide trifluoroacetate.

OFF SLIGHTAXT

A. 7-Methoxy-2-napthalene-sulfonic acid [1-(3-cyanobenzyl)-2-oxopyrrolidin-3-(S)-yl](thlophene-3-ylmethyl)amide. no to beithing at oubiest editions.

The title compound is prepared as described in EXAMPLE 90, Part A using 7-methoxynaphthalene-2-sulfonic acid [1-(3-cyanobenzyl)-2-oxopyrrolidin-3-(S)-yl]amide (0.193 g, 0.44 mmol), prepared as described in EXAMPLE 43, part A, and thiophen-3-ylmethyl bromide (0.30 g, 1.68 mmol). The crude product is

triturated with hexane/ether and used without further purification (0.25 g, 0.48 mmol).

¹H NMR (CDCl₃, 300 MHz) δ 8.45 (s, 1H), 7.94 (AB, 2H), 7.80 (d, 1H), 7.06 (d, 1H), 7.40-7.65 (m, 2H), 7.18-7.32 (m, 4H), 7.05-7.13 (m, 2H), 4.4-4.6 (m, 3H),

- 5 4.38 (AB, 2H), 3.93 (s, 3H), 3.07 (m, 2H), 2.27 (m, 1H), 1.99 (m, 1H). FAB MS, [M+H]+=53200
 - B. 7-Methoxy-2-napthalenesulfonic acid (1-[3-(aminoiminomethyl)benzyl]-2-oxo-3(S)-pyrrolidin-3-yl)(thiophene-3-ylmethyl)amide trifluoroacetate.
- 7-Methoxy-2-napthalenesulfonic acid [1-(3-cyanobenzyl)-2-oxopyrrolidin-3-(S)-yl](thiophen-3-ylmethyl)amide (0.25 g, 0.48 mmol) is converted to the title compound as described in EXAMPLE 24, Part C. The crude product is purified by RP-HPLC eluting with a gradient of 10% CH₃CN/H₂O (0.1% TFA) to 100% CH₃CN/H₂O (0.1% TFA) and the appropriate product fractions are lyophilized to
 - 15 provide the title compound as a white solid (0.150 g, .0.218 mmol).

1H NMR (CD₃OD, 300 MHz) δ 8.48 (s, 1H), 7.97 (d, 1H), 7.88 (m, 2H), 7.6-7.72

(m, 4H), 7:43 (d, 1H), 7:30 (m, 2H), 7:24 (bs, 1H), 6.98 (d, 1H), 4.69 (t, 1H),

- 4.52(AB, 2H), 4.45 (AB, 2H) 3.93 (s, 3H), 3.22 (m, 2H), 2.23 (m, 1H), 2.02 (m, 2H). FAB MS, [M+H]+=549. Elemental analysis calculated with 1 mmol of H₂O
- 20 cal C=52.93 %, H=4.59%, N=8.23%, found C=52.68%, H=4.51%, N=7.97%.

EXAMPLE: 112 The Best of the Section (Section Co., CO., CO.) MARKET

- 6-Methoxynaphthalene-2-sulfonic acid (1-[3-(methoxyaminoiminomethyl)-
- 6-Methoxynaphthalene-2-sulfonic acid [1-(3-cyanobenzyl)-2-oxopyrrolidin-3-(S)-yl]-methylamide, prepared as described in £XAMPLE 25, Part A, (0.096 g, 0.21 mmol) is dissolved in 15 mL of a 2:1 mlxture of EtOH/CH₂Cl₂. The solution is cooled to 0°C and HCl gas is bubbled through the solution for 10 minutes.

 The ice bath is removed and the reaction mixture is stirred at room temperature
- for 18 hours. After this time, the solution is concentrated and pumped under high vacuum until dry. The residue is dissolved in 10 mL of ethanol, and treated in methoxyamine hydrochloride (0.18 g, 2.14 mmol) and triethylatine (0.24 g, 2.38 mmol). The reaction mixture is stirred at room temperature for 24 hours and diluted with ethyl acetate. The organic layer is
- washed with water and brine dried (Na₂SO₄) and concentrated. The residue is purified by flash chromatography eluting with a gradient of 0.25% MeOH/CH₂Cl₂ to 1% MeOH/CH₂Cl₂. The appropriat product fractions are

: 7:

collected, concentrated and converted to the TFA salt to give the title compound (0.41 g, 0.19 mmol) as an amorphous white solid. ¹H NMR (CDCl_s, 300 MHz) δ 8.39 (s₆1H), 7.89 (d, 1H), 7.78 (m, 2H), 7.58 (m, 2H), 7.30 (m, 4H), 6.20 (bs, 2H), 4.88 (t, 1H), 4.42 (AB, 2H), 3.92 (m, 3H), 3.90 5 (m, 3H), 3.21 (m, 2H), 2.75 (m, 3H), 2.22 (m, 1H), 1.95 (m, 1H). FAB MS, 3 [M+H]+=497. Elemental analysis calculated with 1.7 mmol of H₂O cal. C=50.57%, H=5.09%, N=8.74%, found C=50.58%, H=4.55%, N=8.29%.

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EXAMPLE 113

- Broketike in the Committee 6-Methoxynaphthalene-2-sulfonic acid {1-[3-(cyanoaminolminomethyl)benzyl]-2-oxopyrrolidin-3-(S)-yl}methylamide trifluoroacetate. angoin thy 3-6-Methoxynaphthalene-2-sulfonic acid {1-[3-(aminoiminomethyl)benzyl]-2oxopyrrolidin-3-(S)-yl}methylamide (0.2 g, 0.4 mmol), prepared as described in EXAMPLE 25, Part B, is dissolved in ethanol (10 mL), and treated with triethyl amine (0.202 g, 2 mmol) and cyanogen bromide (0.4 mL of a 5 M solution, 2 15 mmol) portionwise over 48 hours. The solution is cooled during the addition of reagents. Upon completion (TLC analysis) the solution is concentrated and the residue purified by chromatography (5% MeOH/CH2Cl2), followed by RP-HPLC eluting with a gradient of 20% CH₃CN/H₂O (0.1% TFA) to 100% CH₃CN/H₂O (0.1% TFA). The title compound is isolated as a white solid (0.043 g, 0.086) mmol).
- ¹H NMR (CD₃OD, 300 MHz) δ 8.42 (s, 1H), 7.97 (d, 1H), 7.85 (d, 1H), 7.72 (m, 3H), 7.42 (m, 3H), 7.30 (d, 1H), 5.00 (m, 1H), 4.48 (AB, 2H), 3.92 (s, 3H), 3.24 (m, 2H), 2.10 (m, 1H), 1.85 (m, 1H). FAB MS, [M+H]*=492. Elemental analysis calculated with 0.6 mmol of H₂O cal. C=59.77%, H=5.26%, N=13.94%, found 25 C=59.75%, H=4.96%, N=13.84%. 45

POPER Common to a service of the control of the con EXAMPLE 114

rocarrage fait d HOI grans Posts for a through 6-Methoxynaphthalene-2-sulfonic acid {1-[3-(hydroxyaminoiminomethyl)benzyll-2-oxopyrrolidin-3-(S)-yl}-methylamide trifluoroacetate. 18 113 30

The residue is used in 10 6-Methoxynaphthalene-2-sulfonic acid [1-(3-cyanobenzyl)-2-oxopyrrolidin-3-(S)-yl]methylamide, prepared as described in EXAMPLE 25, Part A, (0.10 g, 0.22 mmol) is dissolved in 10 mL of methanol, treated with Hydroxylamine hydrochloride (0.078 g, 1.1 mmol) and K₂CO₃ (0.154 g, 1.1 mmol) and heated 35 to reflux for 18 hours. The solution is cooled, concentrated and the residue purified by RP-HPLC eluting with a gradient of 10% CH₃CN/H₂O (0.1%, TFA) to 100% CH_3CN/H_2O (0.1% TFA). The title compound is isolated as a white solid (0.080 g, 0.126 mmol).

¹H NMR (CD₃OD, 300 MHz) δ 8.46 (s, 1H), 8.05 (d, 1H), 7.90 (d, 1H), 7.78 (dd, 1H), 7.62 (m, 3H), 7.58 (m, 1H), 7.50 (m, 1H), 7.38 (dd, 1H), 5.00 (t, 1H), 4.58 (s, 2H), 3.95 (s, 3H), 3.30 (m, 2H), 2.70 (s, 3H), 2.20 (m, 1H), 1.95 (m, 1H). FAB MS, [M+H]*=483. Elemental analysis calculated with 2.1 mmol of H₂O cal. C=48.22%, H=4.90%, N=8.83%, found C=48.86%, H=4.30%, N=8.61%.

EXAMPLE 115

10 4-Amino-3-[3-(S)-(7-methoxynaphthalene-2-sulfonylamino)-2-oxopyrrolidin-1-yl-methyl]benzamidine dihydrochloride.

A.o 4-Amino-3-methylbenzonitrile. Subtract of the State o

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To a solution of 3-methyl-4-nitrobenzonitrile (2 g, 12.3 mmol) in 100 mL of

- 15 EtOH is added SnCl₂ (13.9 g, 61.7 mmol). The resulting solution is refluxed. After 2 hours, the solution is cooled to amblent temperatures. The solution is poured into 150 mL of ice water. The pH of the solution is adjusted to >7 with a solution of saturated NaHCO₃. The solution is diluted with EtOAc and the resulting mixture is filtered through Celite. The filtered solution is separated.
- The organic layer is dried over MgSO₄, filtered and concentrated to give the title compound (1.57 g, 8.7 mmol) as an off-white solid.

 ¹H NMR (CDCl₃, 300 MHz) δ 7.30 (m, 2H), 6.63 (d, 1H), 4.10 (bs, 2H), 2.15 (m, 2H). El MS, [M]*=132.
- B. 4-(Benzhydrylidenylamino)-3-methylbenzonitrile.

 To a solution of 4-amino-3-methybenzonitrile (1.2 g, 9.08 mmol) in 75 mL of toluene is added benzophenone (1.74 g, 9.53 mmol) and p-toluenesulfonic acid (0.43 g, 2.1 mmol). The reaction vessel is fitted with a Dean-Stark trap and the solution is heated to reflux. After 24 hours, the solution is cooled to ambient temperatures. The solution is concentrated. The crude material is purified by column chromatography eluting with a gradient of 3% EtOAc/hexañes to 10% EtOAc/hexañes. The title compound (2.43 g, 8.2 mmol) is obtained as an oil.

 14 NMR (CDCl₃, 300 MHz) 8 7.80 (m, 2H), 7.40 (m, 6H), 7.30 (s, 1H), 7.15 (d, 35 1H), 7.05 (bs; 2H), 6.50 (d, 1H), 2.20 (s, 3H). El MS, [M] = 296.
 - a.21 in a strained as a cliew and.

C. 4-(Benzhydrylidenylamino)-3-bromomethylbenzonitrile.

D. {1-[2-(Benzhydrylidenylamino)-5-cyano-benzyl]-2-oxopyrrolidin-3-yl}-carbamic acid tert-butyl ester. los medchin-t-lydis m-8 fo moliulos s of

The title compound is prepared as described in EXAMPLE 23, Part B substituting 4-(benzhydrylidenylamino)-3-bromomethylbenzonitrile for α-bromo-m-toluyl nitrile. The crude material is purified by column oc chromatography eluting with a gradient of 30% EtOAc/ hexanes to 40% EtOAc/hexanes. The title compound is obtained as a yellow solid.28

20, 3H NMR (CDCl₃, 300 MHz), § 7.70 (bs, 2H), 7.40 (s, 1H), 7.38 (bs, 6H), 7.30 (d, 1H), 7.15 (bs, 2H), 6.48 (d, 1H), 5.00 (d, 1H, 4.45 (AB, 2H), 4.15 (m, 1H), 3.30 (m, 2H), 2.61 (m, 1H), 1.90 (m, 1H), 1.45 (s, 9H).

Oxopyrrolidin-3-yllamide.

Hydrogen chloride gas is bubbled through a solution of {1-[2-]

(benzhydrylidenylamino)-5-cyanobenzyl]-2-oxopyrrolidin-3-yl)carbamic acid

tert-butyl ester (0.70 g, 1.42 mmol) in 75 mL of EtOAc at 0°C for 5 minutes.

After 1 hour, the solution is concentrated. The resulting residue is dissolved in

50 mL of CH-CN. To the solution is added triethyl amine (0.79 mL; 5.68 mmol)

and 7-methoxynaphthalene sulfonyl chloride (0.38 g, 1.49 mmol). After 5

hours, the reaction mixture is diluted with EtOAc. The resulting solution is

washed with saturated NaHCO3 and saturated NaCl. The organic layer is dried

over MgSO4, filtered and concentrated. The crude material is purified by

column chromatography eluting with 5% CH3OH/CH2Cl2. The title compound

(0.60 g, 1.21 mmol) is obtained as a yellow solid.

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¹H NMR (CDCl₃, 300 MHz) δ 8.30 (s, 1H), 7.90 (d, 1H), 7.80 (d, 1H), 7.70 (d, 1H), 7.35 (m, 4H), 6.55 (d, 1H), 5.25 (d, 1H), 4.90 (s, 2H), 4.30 (AB, 2H), 3.95 (s, 3H), 3.75 (m, 1H), 3.20 (m, 2H), 2.55 (m, 1H), 2.00 (m, 1H).

5 F 4-Amino-3-[3-(S)-(7-methoxynaphthalene-2-sulfonylamino)-2-oxopyrrolidin-1-yl-methyl]benzamidine dihydrochloride.

7-Methoxynaphthalene-2-sulfonic acid [1-(2-amino-5-cyano-benzyl)-2-oxopyrrolidin-3-yl]amide is converted to the title compound as described in EXAMPLE 24, Part C. The crude product is purified by RP-HPLC eluting with a gradient of 10% CH₃CN/H₂O to 60% CH₃CN/H₂O and the appropriate product fractions are lyophilized to provide the title compound as a white solid.

¹H NMR (DMSO-d₆, 300 MHz) δ 8.80 (bs, 2H), 8.45 (bs, 2H), 8.35 (s, 1H), 8.10 (d, 1H), 8.00 (d, 1H), 7.90 (d, 1H), 7.70 (dd, 1H), 7.50 (m, 2H), 7.40 (d, 1H), 7.35 (dd, 1H), 6.70 (d, 1H), 6.20 (bs, 2H), 4.15 (AB, 2H), 4.10 (m, 1H), 3.90 (s, 3H),

15 3.12 (m, 2H), 1.98 (m, 1H), 1.55 (m, 1H). Elemental analysis calculated with 2 mmol of H₂O calc C=47.92%, H=5.42%, N=12.15%, found C=48.00%, H=5.27%, N=12.29%. The review of eliminate of the second control of the se

EXAMPLE 116 TO MOBILE A

A.S. (1-12-(Benzhydrylidenylamino)-5-cyano-benzyli-2-oxopyrrolidin-3-yl}-N-methylcarbamic acid tert-butyl ester.

- To a solution of [1-[2-(benzhydrylldenylamino)-5-cyanobenzyl]-2-oxopyrrolidin-3-ŷl)carbamic acid tert-butyl ester (3.94 g, 7.98 mmol) in 8 mL of DMF at 0°C is added a 60% mineral oil dispersion of NaH (0.35 g, 8.77 mmol). After 20 minutes, methyl iodide (0.99 mL, 15.9 mmol) is added. After 2 hours, the solution is diluted with saturated NH₄Cl and EtOAc. The layers are separated.
- dried over MgSO₄, filtered and concentrated. The crude material is purified by column chromatography eluting with a gradient of 30% EtOAc/ hexanes to 50% EtOAc/hexanes. The title compound (3.72 g. 7.31 mmol) is obtained as a yellow solid.
 - 35 H NMR (CDCl₃, 300 MHz) 8 7.70 (bs, 2H), 7.45 (m, 8H), 7.10 (bs, 2H), 6.45 (dd, 1H), 4.70 (m, 1H), 4.49 (AB, 2H), 3.30 (m, 2H), 2.83 (s, 3H), 2.35 (m, 1H), 2.10 (m, 1H), 1.50 (s, 9H). FAB MS, [M+H] = 509.

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'급 NM점 (CDC), 309 NH2, 1호 69 G 러워, 기억) (d, 1점) 7,95 (d 14). 7-Methoxynaphthalene-2-sulfonic acid [1-(2-amino-5-cyanobenzyl)-2-OH), E 78 (m. 1H), 3.20 (m, 2H), 2.5. Spinshylamide, 3.20 (m, 2H), 3.20 (m, 2H), 3.20 (m, 2H), 3.5. The title compound is prepared as described in EXAMPLE 115, Part E substituting [1-[2-(benzhydrylidenylamino)-5-cyanobenzyl]-2-oxopyrrolidin-3yl}-N-methylcarbamic acid tert-butyl ester for {1-[2-(benzhydrylidenylamino)-5cyanobenzyl]-2-oxopyrrolidin-3-yl}carbamic acid tert-butyl ester.: The title compound is obtained as a yellow solid. a shimally-C-n bilonyquan 1H NMR (CDCI₃, 300 MHz) δ 8.38 (s, 1H), 7.87 (d, 1H), 7.78 (d, 1H), 7.72 (dd, 1H), 7.32 (dd, 1H), 7.30 (dd, 1H), 7.28 (d, 1H), 7.23 (dd, 1H), 6.55 (d, 1H), 4.98 He product (s, 2H), 4.25 (AB, 2H), 4.15 (m, 1H), 3.98 (s, 3H), 3.20 (m, 2H), 2.70 (s, 3H), 11 NMP (DMSO-d_a, 200 MHz) & 8.30 (bs, 2H), 8.45 (bs, 2H), 8.15 (5 (d. 1H), 8.00 (d, 1H), 7:90 (d, 1H), 7.70 (dd, 1H), 7.50 (m, 2H), 7.40<u>1</u> d. (d), 7.35 Amino-3-[3-(S)-(7-methoxynaphthalene-2-sulfonylmethylamino)-2-Oxopyrrolidin-1-ylmethyllbenzamidine trifluoroacetate. (HIS mil Si & 7-Methoxynaphthalene-2-sulfonic acid [1-(2-amino-5-cyano-benzyl)-2oxopyrrolidin-3-yl]methylamide is converted to the title compound as described in EXAMPLE 24, Part C. The crude product is purified by RP-HPLC eluting with a gradient of 10% CH₃CN/H₂O (0.1% TFA) to 60% CH₃CN/H₂O (0.1% TFA) and the appropriate product fractions are lyophilized to provide the title compound as a white solid. as a white solid, telepropular, embrassed τ μεσυν-1-οίο σανάσκο ¹Η ΝΜΡ (DMSO-d_e, 300 MHz) δ 8.90 (bs, 2H), 8.75 (bs, 2H), 8.40 (s, 1H), 8.050 (d, 1H), 7.95 (d, 1H), 7.70 (dd, 1H), 7.60 (d, 1H), 7.55 (dd, 1H), 7.48 (d, 1H), 7.39 (dd, 1H), 6.70 (d, 1H), 6.00 (bs, 1H), 4.98 (m, 1H), 4.20 (AB, 2H), 3.90 (s, 3H), 3.15 (m, 2H), 2.67 (s, 3H), 2.05 (m, 1H), 1.70 (m, 1H). FAB MS, [M+H]+=482. Elemental analysis calculated with 1.3 mmol of H2O cal. C=50.49%, H=4.98%, N=11.32%, found C=50.50%, H=4.50%, N=10.99%.

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column chromategrachy alpling with a aradiant of 32% EtC revances to 50% N-(4-Cyano-2-(3-[(7-methoxynaphthalene-2-sulfonyl)methylamino]-2oxopyrrolidin-1-ylmethyl)phenyl)acetamide.

To a solution of 7-methoxynaphthalene-2-sulfonic acid [1-(2-amino-5-cyanobenzyl)-2-oxopyrrolidin-3-yl]methylamide (0.28 g, 0.61 mmol), prepared as described in EXAMPLE 116, Part B, in 25 mL of CH2Cl2 is added triethyl amine

1. 9. H.

(0.25 mL, 1.81 mmol), dimethylamino pyridine (0.01 g, 0.061 mmol), and acetyl chloride (0.43 g, 6.05 mmol). The solution is heated to 60°C. After 16 hours, The solution is cooled to ambient temperatures and diluted with EtOAc. The solution is washed with saturated NaHCO₃ and saturated NaCl. The organic layer is dried over MgSO₄, filtered and concentrated. The crude material is purified by column chromatography eluting with 20% EtOAc/CH₂Cl₂. The title compound (0.232 g, 0.49 mmol) is obtained as a white solid. ¹H NMR (CDCl₃, 300 MHz) δ 9.50 (s, 1H), 8.50 (d, 1H), 8.30 (s, 1H), 7.89 (d, 1H), 7.80 (d, 1H), 7.76 (dd, 1H), 7.60 (d, 1H), 7.40 (d, 1H), 7.20 (m, 2H), 4.90 (m, 1H), 4.30 (AB, 2H), 3.90 (s, 3H), 3.30 (m, 2H), 2.75 (s, 3H), 2.35 (m, 1H), 2.05 (m, 1H), 1.90 (s, 3H).

B. N-(4-Carbamimidoyl-2-{3-[(7-methoxynaphthalene-2-sulfonyl)methyl-amino]-2-oxopyrrolidin-1-(S)-ylmethyl)phenyl)acetamide trifluroacetate.

- N-(4-Cyano-2-{3-{(7-methoxynaphthalene-2-sulfonyl)methylamino]-2-oxopyrrolidin-1-ylmethyl)phenyl)acetamide is converted to the title compound as described in EXAMPLE 24, Part C: The crude product is purified by RP-HPLC eluting with a gradient of 10% CH₃CN/H₂O (0.1% TFA) to 60% CH₃CN/H₂O (0.1% TFA) and the appropriate product fractions are lyophilized to provide the title compound as a white solid.
- ¹H NMR (DMSO-d₆, 300 MHz) δ 9.70 (s, 1H), 9.23 (bs, 2H), 9.00 (bs, 1H), 8.40 (s, 1H), 8.00 (d, 1H), 7.98 (d, 1H), 7.70 (m, 2H), 7.60 (m, 2H), 7.35 (dd, 1H), 4.97 (m, 1H), 4.40 (AB, 2H), 3.90 (s, 3H), 3.20 (m, 2H), 2.68 (s, 3H), 2.10 (m, 1H), 2.00 (s, 3H), 1.80 (m, 1H). FAB MS, [M+H]*=524. Elemental analysis calculated with 1.5 mmol of H₂O cal. C=50.60%, H≥5.00%, N=10.54%, found

C=50.48%, H=4.61%; N=10.17%as this as all tradument outlined tychiened at the state of the stat

EXAMPLE 118

து நடிக்கு நடிக்கு கட்டு கி.பி. பெரியில் கடிக்க மி.பி. இது நடிக்கும் கடிக்கி தி. <u>A. 4-tert-Butylbenzene-2-sulfonic acid [1-(2-amino-5-cyano-beńzyl)-2-</u> நடிக்கு (DOD), 300 Md2) நோர் (பி.இ.ந.) இது மெற்றார்கள்

35 tert-butyl sulfonyl chloride in place of 7-methoxynaphthalene sulfonyl chloride.

The title compound is prepared as described in EXAMPLE 115? Part E, using tert-butyl sulfonyl chloride in place of 7-methoxynaphthalene sulfonyl chloride.

The title compound is obtained as a yellow solid and the compound is obtained as a yellow solid and the compound is obtained as a yellow solid and the compound is prepared as described in EXAMPLE 115? Part E, using tert-butyl sulfonyl chloride.

14 NMR (CDCl₃, 300 MHz) δ 7.80 (d, 2H), 7.55 (d, 2H), 7.35 (dd, 1H), 7.25 (d, .51100 6 11H), 6.60 (d, 1H), 5.15 (s, 1H), 4.90 (s, 2H), 4.28 (AB, 2H), 3.75 (m, 1H), 3.20 en of (m; 2H), 2:55 (m; 1H), 2:03 (m; 1H), 1:30 (s; 9H), 9100 e notitulo è en i solution is washed with saturated NaHCO, and saturated NaOL. The organing 21 5 10 Br 4-Amino-3-[3-(S)-(4-tert-butylbenzeriesulfonvlamino)-2-oxopyrrolidin-1-ylpurified by column chromatograistates and intermined by column chromatograistates and purified by column chromatog 4-tert-Butylbenzene-2-sulfonic acid [1-(2-amino-5-cyanobenzyl)-2-0 E) 83 oxopyrrolidin-3-yl]amide is converted to the title compound as described in 08.4 (EEXAMPLE 24) Part C. The crude product is purified by RP-HPLC eluting with a 10 gradient of 10% CH₃CN/H₂O (0.1% TFA) to 60% CH₃CN/H₂O (0.1% TFA) and the appropriate product fractions are lyophilized to provide the title compound as a white solid. H NMR (DMSO-d, 300 MHz) 8 8.80 (\$, 1H), 8.30 (bs, 2H), 8.05 (a, 1H), 7.80 6.20 (bs, 2H), 7.60 (d, 2H), 7.50 (d, 1H), 7.40 (s, 1H), 6.70 (d, 1H), 6.20 (bs, 2H), 4.20 -(AB, 2H); 4.10 (m; 1H); 3.15 (m) 2H); 2.05 (m, 1H), 1.50 (m, 1H), 1.25 (s, 9H). FAB MS: [M+H]*=444: Elemental analysis calculated with 0.5 mmol of excess TFA cala C=48.86%, H=5.00%, N=11.39%, Found C=49.10%, H=5.21%, HPLO shang with a gradient of 10% CH3ON/H2O (0.1% TS% 36.16 = 0.14 CH2O H H.O (0.1% TEA) and the appropriate product frections are tyophilized to **EXAMPLE 119** provide the rille compound as a white solid. 1.8 H 3-Amino-5-[3-(S)-(7-methoxynaphthalene-2-sulfonylamino)-2-oxopyrrolidin-1-Hi , yl-methyl]benzamidine bistrifluoroacetate,b) 89.7 (Ht .b) 00.8 (Ht .b) 4.97 (m, 111), 4.40 (AB, 2H), 3.90 (s, 3H), 3.20 (m. 2H), 2.68 (s, 3H), 2.10 cm. 181), 23.00 (c. 334), 4.80 (m, 4H). FAR. eliîtinôżnedlydtem-č-onimA-E-1/8.6 1,25). The title compound is prepared as described in EXAMPLE 115, Part A using 3methyl-5-nitro-benzonitrile as the starting material. 15 4-11 (23) GR= 3 $^{1}\text{H NMR (CDCl}_{3}$, 300 MHz) δ 6.83 (s, 1H), 6.70 (s, 1H), 6.68 (s, 1H), 3.70 (bs, 2H), 2.30 (s. 3H). 4-Amino-3-13-15 (4-rest-butylbanzanesyllogylamine: 2-propyriolidic 1 ve B. 3-(Benzhydrylidenylamino)-5-methylbenzonitrilenining son Tigdtem The title compound is prepared as described in EXAMPLE 115, Part B, using 3-amino-5-methylbenzonitrile in place of 4-amino-3-methylbenzonitrile. ¹H NMR (CDCl₃, 300 MHz) δ 7.73 (d, 2H), 7.45 (m; 2H), 7.30 (m; 4H), 7.05 (dd, 2H), 7.00 (s, 1H), 6.78 (s, 2H), 6.71 (s, 1H), 2:20 (s, 3H). EI'MS, [M] =296. tember of suffernyl chlorice in piace of 7-methoxynaphiticlenie sulfang, thicker C. 3-(Benzhydrylidenylamino) 5-bromomethylbenzonitrile. 100 still to 37

The title compound is prepared as described in EXAMPLE 115, Part C using 3-(benzhydrylidenylamino)-5-methylbenzonitrile as the starting material.
¹H NMR (CDCl₃, 300 MHz) δ 7.75 (d, 2H), 7.50 (m, 1H), 7.40 (m, 2H), 7.30 (m, 4H), 7.05 (m, 2H), 6.95 (s, 1H), 6.89 (s, 1H), 4.30 (s, 2H). El MS, [M]*=374.

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D. (1-[3-(Benzhydrylidenylamino)-5-cyano-benzyl]-2-oxopyrrolidin-3-yl}-carbamic acid tert-butyl ester.

The title compound is prepared as described in EXAMPLE 23, Part B substituting 3-(benzhydrylidenylamino)-5-bromomethylbenzonitrile for co-

bromo-m-toluyl nitrile. The crude material is purified by column chromatography eluting with a gradient of 30% EtOAc/ hexanes to 40% EtOAc/hexanes. The title compound is obtained as a yellow solid.

1H NMR (CDCI₃, 300 MHz) δ 7.75 (d, 2H), 7.50 (m, 1H), 7.40 (m, 2H), 7.30 (m, 4H), 7.10 (m, 1H), 6.95 (s, 1H), 6.65 (s, 1H), 5.10 (bs, 1H), 4.30 (AB, 2H), 4.05 (m, 1H), 3.85 (m, 2H), 2.55 (m, 1H), 1.75 (m, 1H), 1.40 (s, 9H). El MS, [M]*=495.

E:#7-Methoxynaphthalene-2-sulfonic acid [1-(3-benzhydrylidenylamino-5-cyanobenzyl)-2-oxopyrrolidin-3-yllamide.

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The title compound is prepared as in EXAMPLE 115, Part E, substituting {1-[3-20 (benzhydrylidenylamino)-5-cyanobenzyl]-2-oxopyrrolidin-3-yl}carbamic acid tert-butyl ester for {1-[2-(benzhydrylidenylamino)-5-cyanobenzyl]-2-oxopyrrolidin-3-yl}carbamic acid tert-butyl ester.

1H NMR (CDCl₃, 300 MHz) δ 8.35 (s, 1H), 7.90 (d, 1H), 7.80 (d, 1H), 7.75 (dd, 1H), 7.70 (d, 2H), 7.50 (m, 1H), 7.40 (m, 2H), 7.25 (m, 5H), 7.00 (m, 4H), 6.55 (s,

25 1H), 5.25 (s, 1H), 4.25 (AB, 2H), 3.95 (s, 3H), 3.65 (m, 1H), 2.80 (m, 2H), 2.45 (m, 1H), 1.95 (m, 1H). FAB MS, [M+H]+=615. (m, 2H), 2.80 (m, 2H), 2.45 (m, 2H), 1.95 (m, 2H). See a solution to the blue as from See as from See a solution to the blue as from See as from See a solution to the blue as from See as from S

E 3-Amino 5-[3-(S)-(7-methoxynaphthalene-2-sulfonylamino)-2-oxopyrrolidin-1-vi-methyllbenzamidine bistrifluoroacetate.

7-Methoxynaphthalene-2-sulfonic acid [1-(3-benzhydrylidenylamino-5-cyano-benzyl)-2-oxopyrrolidin-3-yl]amide is converted to the title compound as described in EXAMPLE 24, Part C. The crude product is purified by RP-HPLC feluting with a gradient of 10% CH₃CN/H₂O (0.1% TFA) and the appropriate product fractions are lyophilized to provide the title compound as a white solid.

1H NMR (DMSO-d_s, 300 MHz) 8 9.15 (s, 1H), 9.00 (bs, 2H), 8.35 (s, 1H), 8.20 (d, 1H), 8.05 (d, 1H), 7.95 (d, 1H), 7.70 (dd, 1H), 7.60 (d, 1H), 7.20 (dd, 1H), 6.70

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35

(s, 1H), 6.65 (s, 1H), 6.60 (s, 1H), 5.80 (bs, 2H), 4.20 (AB, 2H), 4.10 (m, 1H), ::3.90 (s, 3H), 3.00 (m, 2H), 2.00 (m, 1H), 1.50 (m, 1H); EAB MS, [M+H]+=468. Elemental analysis calculated with a mmol of excess TFA cal. C=43.02%, 47. H=3.49%, N=8.65%, found C=43.51%, H=3.82%, N=8.89% 7 (H)

alk or indicate 220 - live and one good (on many ability investment) - E. C. O. [4-(Aminoiminomethyl)-2-[3-(7-methoxynaphthalene-2-sulfonylamino)-2oxopyrrolidin-1-ylmethyl]phenoxylacetic acid methyl ester trifluoroacetate.

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A. 4-Hydroxy-3-methylbenzonitrile, page 1867. All the control of t To a solution of 4-bromo-3-methylbenzonitrile (7.07 g, 36.1 mmol) in 225 mL of THE at -78°C is added a 1.7 M solution of tent-butyl lithium (45.6 mL, 77.6 mmol) in pentane. After 5 minutes, CuBr-SMe₂ (15.9 g, 77.6 mmol) is added. The resulting solution is stirred for 10 minutes, then O2 is slowly bubbled through the reaction mixture for 30 minutes. After this time, the solution is: allowed to warm to ambient temperatures. The solution is stirred for 16 hours. The solution is then poured into 100 mL of H₂O₃₁ The solution is diluted with EtOAc. The layers are separated. The organic layer is washed with saturated NH4SO4 solution. The organic layer is then extracted with 10 N NaOH. The collected aqueous basic layers are acidified to pH=6 with 6N HCl.eThe solution is then extracted with EtOAc. The combined organic layers are dried over MgSO₄, filtered and concentrated. The title compound is obtained as a solid. .¹H NMR₃(CDCl₃, 300 MHz) δ 9.00 (s. 1H), 7.45 (s. (1H), 7.40 (d. 1H), 6.8c (d. 1H), 2.26 (s, 3H). ELMS, [M]+ 133. √ (ALB (n) OF 5 (ALB (b) ON 5 (H)

5.25 (1) (110) 4.25 (A.3) 9HN 3.35 (a) 3H) 3/65 (ct. 111), 2.60 22 (4-Cyano-2-methylphenoxy)acetic acid methyl ester. 29 HI 49 Methyl bromoacetate (0.56 mL, 5.92 mmol) is added to a solution of phenol (0.70 g, 5.29 mmol), K₂CO₃ (1.6 g, 11.6 mmol) and tetrabutyl ammonium iodide (0.57 g, 1.53 mmol) in 30 mL of DMF. The resulting solution is heated to 80°C **30** for 16 hours. The solution is then cooled to ambient temperatures. The solution is diluted with EtOAc. The resulting solution is washed with H2O and saturated NaCl. The organic layer is dried over MgSO, filtered and all concentrated. The crude product is purified by column chromatography eluting with a gradient of 10% EtOAc/hexanes to 50% EtOAc/hexanes to afford the title compound (1.4 g, 0.8 mmol). title compo and as a white solld.

¹H NMR (CDCl₃, 300 MHz) δ.7.45 (m, 2H), 6.70 (d, 1H), 4.68 (s, 2H), 3.80 (s, 2H), 2.25 (s, 3H). EI MS, [M]+=205.

- C. (2-Bromomethyl-4-cyanophenoxy)acetic acid methyl ester.

 The title compound is prepared as described in EXAMPLE 115, Part C, substituting (4-cyano-2-methylphenoxy)acetic acid methyl ester for
- 4-(benzhydrylidenylamino)-3-methylbenzonitrile. The title compound is obtained as a white solid.
 ¹H NMR (CDCl₃, 300 MHz) δ 7.65 (d, 1H), 7.55 (dd, 1H), 6.80 (d, 1H), 4.80 (s, 2H), 4.55 (s, 2H), 3.80 (s, 3H). EI MS, [M]*=283.
- 10 D. [2-(3-tert-Butyoxycarbonylamino-2-oxopyrrolidin-1-ylmethyl)-4-cyano-phenoxylacetic acid methyl ester.

The title compound is prepared as described in EXAMPLE 23, Part B, substituting (2-bromomethyl-4-cyanophenoxy) acetic acid methyl ester for α-bromo-m-toluylnitrile. The title compound is obtained as a white solid.

15 [H NMR (CDCl₃, 300 MHz) δ 7.55 (m, 2H), 6.78 (d, 1H); 5.10 (bs, 1H), 4.70 (s, 2H), 4.55 (AB, 2H), 4.15 (m, 1H), 3.80 (s, 3H), 3.20 (m, 2H), 2.60 (s, 2H), 1.90 (m, 1H), 1.58 (s, 9H).

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- E. (4-Cyano-2-[3-(7-methoxynaphthalene-2-sulfonylamino)-2-oxopyrrolidin-1-
- 20. <u>ylmethyl]phenoxy}acetic acid methyl ester.</u>

 The title compound is prepared as described in Example 115, Part E substituting (2-bromomethyl-4-cyanophenoxy)acetic acid methyl ester for {1-[2-(benzhydrylidenylamino)-5-cyanobenzyl]-2-oxopyrrolidin-3-yl}carbàmic acid tert-butyl ester. The title compound is obtained as a white foam?
 - 25____H NMR (CDCl₃: 300 MHz)-δ(8:35-(s, 1H), 7.90*(d, 1H); 7:75 (dd, 1H), 7.55 (dd, 1H), 7.42 (d, 1H), 7.30 (dd, 1H), 7.20 (m, 1H), 6.70 (d, 1H), 5.40 (d, 1H), 4.65 (s, 2H), 3.95 (s, 3H), 3.70 (m, 1H), 3.20 (m, 2H), 2.50 (m, 1H), 2.05 (m, 1H). FAB MS, [M+H]*=524.

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- F. {4-(Aminoiminomethyl)-2-[3-(7-methoxynaphthalene-2-sulfonylamino)-2-oxopyrrolidin-1-ylmethyl]phenoxy)acetic acid methyl ester trifluoroacetate.

 The title compound is prepared as described in EXAMPLE 32; Part C, substituting {4-cyano-2-[3-(7-methoxynaphthalene-2-sulfonylamino)-2-oxopyrrolidin-1-ylmethyl]-phenoxy)acetic acid methyl ester for of 7-2-oxopyrrolidin-1-ylmethyl]-phenoxy)acetic acid methyl ester for of 7-2-oxopyrrolidin-1-ylmethyll-phenoxy)acetic acid methyl ester for of 7-2-oxopyrrolidin-1-ylmethyll-phenoxy)acetic acid methyllester for of 7-2-oxopyrrolidin-1-ylmethyll-phenoxy)acetic acid methyllester for other formal for acid methyllester for other formal for
- 35. Hbenzyloxynaphthalene-2-Sülfönichacid [1-(3-cyānöbenzyl)-2-oxopyrrolidin-3-(S)-yl]amide. The title compound is obtained as a white solid. (1999) (1999) (1999)

 $^{1}\text{H NMR (DMSO-d}_{8}$, 300 MHz) δ 9.00 (bs, 4H), 8.30 (s, 1H), 7.97 (d, 1H), 7.90 (d, 1H), 7.65 (m, 2H), 7.50 (s, 1H), 7.37 (s, 1H), 7.25 (dd, 1H), 7.10 (d, 1H), 4.95 (AB, 2H), 4:30 (AB, 2H), 4:05 (m, 1H), 3:80 (s, 3H), 3:60 (s, 3H), 3:15 (m, 2H), 1.95 (m, 1H), 1.55 (m; 1H): (FAB MS, [M+H]*=541. Elemental analysis 5 to calculated with: 3.4 mmol of H2O cal C=46.98%, H=5.04%, N=7.83%, found C=46.99%, H=4.84%, N=8.10%. obtained as a unite solid. 14 NIME, CENCH, 300 MHZ) \$7.85 (J. 14), 7.65 (do. 15), 8.80 (d. 15), 4 J. **EXAMPLE 121** 2H, 4.55 (s, 5 c), 5.67 (s, 6H) of MS. [M] =233. 4-(Aminoiminomethyl)-2-[3-(7-methoxynaphthalene-2-sulfonylamino)-2-10 oxopyrrolidin-1-ylmethyl]phenoxy}acetic acid trifluoroacetate. phenoxylecetic acid methyl estet. To a solution of {4}(aminoiminomethyl)-2-[3-(7-methoxynaphthalene-2sulfonylamino)-2-oxopyrrolidin-1-ylmethyl]-phenoxy)-acetic acid methyl ester trifluoroacetate (0.1:g; 0:18 mmol), prépared as in EXAMPLE 120, Part E, in 2 3 15 (mL of EtOH is added 10 N NãOH (0.05 mL). The solution is stirred for 5 hours. After this time; the solution is concentrated. The residue is dissolved in 2 mL of H₂O and the pH is adjusted to 3 using 1 N HCl. The solid which forms is collected by filtration. The solid is purified by RP-HPLC eluting with a gradient of 10%CH₃CN/H₂O (0.1% TFA) to 100% CH₃CN. The appropriate fraction are lyophilized to afford the title compound (0.05 g; 0.7 mmol) as a white solid. 1H NMR (DMSO₅d₆, 300 MHz) δ 9.10 (bs, 2H), 8.70 (bs, 2H), 8.35 (s, 1H), 8.15 (d, 1H), 8.00 (d, 1H), 7.90 (d, 1H), 7.70 (m, 2H), 7.50 (s, 1H), 7.45 (s, 1H), 7.30 tios cons(m, 1H), 7.10 (m, 1H), 4.85 (s, 1H), 4.30 (AB, 2H), 4.05 (m, 1H), 3.80 (s, 3H), 3.10₍(m, 2H), 1.95₍(m, 1H), 1.55 (m, 1H). FAB MS; [M+H]*=527. Elemental 25 analysis cal.; C=46.16%, H=3.74%; N=7.42%; found C=45.98%, H=3.87%, 14; 7 42 (d 14), 7.30 (dd 11), 7.80 (m 16), 7.70 (d, 18), **%7.75.** (1 14) 2H) See e. 3H), 3E0 (m, 1H), 3E0 (m, Fel), 850 (m, 1H), ZU5 (m, 1H) & V **EXAMPLE 122** 4-(3-Amino-2-oxo-pyrrolidine-1-ylmethyl)thiophene-2-carbonitrile 30, hydrochloride of andor axadience of the land normalimeters. O. sany of the extra conformation and add authority of a little consiste. A. 5-lodothiophene-3-carboxaldehydemaqena a bnaacan a still edil To a solution of thiophene, 3 carboxaldehyde (36:g, 321 mmol) in 80 mL of CCI, and 60 mL of H2O is added 2.5 mL of conc. H2SO4 in 160 mL of acetic 35 acid. To the resulting solution is added HIO (14 g. 80 mmol) and is (38 g. 150 mmol). The solution is refluxed for 6 hours. After this time, the reaction is

cooled to ambient temperatures and 200 mL of CHCl₃ is added. The layers are

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separated. The aqueous layer is extracted with CHCl₃. The organic layers are combined and washed with 0.5 M Na₂S₂O₃, sat. NaHCO₃ and sat. NaCl. The organic layer is dried over MgSO₄, filtered and concentrated. The crude product is purified by column chromatography eluting with gradient of 2%

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5 EtOAc/ hexanes to 5% EtOAc/hexanes to afford the title compound (20 g, 84 mmol) as a white solid.

1H NMR (CDCI_a, 300 MHz) δ 9.78 (s, 1H), 8.10 (s, 1H), 7.69 (s, 1H).

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B: (5-lodothiophene-3-ŷl)methanol.

- To a solution of 5-iodothiophene-3-carboxaldehyde (42 g, 176 mmol) in 800 mL of THF is added NaBH₄ (7 g, 185 mmol). After 1hour, the reaction is quenched by the addition of 100 mL of sat NH₄Cl. The resulting solution is diluted with 1 L of EtOAc. The layers are separated. The organic layer Is washed with H₂O and sat. NaCl. The organic layer is dried over MgSO₄, filtered and concentrated. The title compound (42 g, 175 mmol) is obtained as an oil.
 - ¹H NMR (CDCl₃, 300 MHz) δ 7.18 (s, 2H), 4.63 (s, 2H), 1.92 (bs; 1H).

C. 4-Hydroxymethylthiophene-2-carbonitrile.

To a solution of (5-iodothiophene-3-yl)methanol (42 g, 176 mmol) in 150 mL of 20. DMF is added Zn(CN)₂ (12.4 g, 106 mmol) and Pd(PPh₃)₄ (8.13 g, 7.04 mmol). The solution is heated to 80°C. After 6 hours, the solution is diluted with 3 L of EtOAc. The resulting solution is washed with 1N NH₄OH, H₅O and sat. NaCl.

EtOAc. The resulting solution is washed with TN NH₄OH, H₂O and sat. Naci.

a product is purified by column chromatography eluting with gradient of 20%

25 \ EtoAc/ hexanes to 30% EtoAc/ hexanes to afford the title compound (10 g, 72 and a minol) as a clear bill or the minol of the compound of the minol of the m

948 (a) Salt (att ,m) 581 (H; ,m) 8618 (H; ,m) 75 6 (H; ,m) 5° + ,049

To a solution of 4-hydroxymethylthiophene-2-carbonitrile (10 g, 72 mmol), in 360 mL of THF is added triphenyl phosphine (18.3 g, 76 mmol) and CBr₄ (25 g, 76 mmol). After 3 hours, the solution is filtered and concentrated. The crude product is purified by column chromatography eluting with gradient of 5%

EtOAc/ hexanes to 10% EtOAc/hexanes to afford the title compound (14 g, 69 mmol) as a white solid.

1H NMR (CDCI₃, 300 MHz) δ 7.62 (s, 1H), 7.49 (s, 1H), 4.42 (s, 2H).

septimiles. The aquecus level is earn steel to SeiOu. The projenic is yous a E. (2-Oxopyrrolidin-3-(S)-yl)carbamic acid tert-butyl ester. Andicimos (S)-Boc-Diaminobutyric acid (25 g, 115 mmol), triethyl amine (35 g, 344 mmol), and hydroxybenzotriazole (19.3 g, 143 mmol), are dissolved in 300 mL of THF. 5 1-(3-Dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (27.4g. 143 mmol) is added to the solution. The solution is heated to:60°C over 15 minutes. A white precipitate forms and the solution is kept at 60°C for 4 hours. After this time, the solution is filtered and the collected liquid is concentrated. The crude product is purified by column chromatography in a gradient of 1% MeOH/CH2Cl2 to 3% MeOH/CH2Cl2 to afford the title compound (19.6 g, 98 mmol) as a white solid. (form 88 man), HBs wedder at HF is udded NaBH, (Tig. 185 man). 1H NMR (CDCI₃, 300 MHz) δ 6.17 (bs., 1H), 5.08 (bs., 1H), 4.12 (m, 1H), 3.33 (m, 2H), 2.65 (m, 1H), 2.00 (m, 1H), 1.42 (s, 9H). ACIB (c) Wagner with 4.0 and set Mod. The organic layer is uned the O.F. (1999). The F. In-(5-Connection) F. [1-(5-Cyanothiophene-3-ylmethyl)-2-oxopyrrolidin-3-yl]carbamic acid tert-191 NMR (CDC), 300 MHz) & 7.13 (s. 2H), 4.63 (s. 2H), 1. Telson Multiple To a solution of (2-oxopyrrolidin-3-(S)-yl)carbamic acid tert-butyl ester (3.2 g, 16 mmol) in 80 mL of THF:DMF (10:1) at 0°C is added 4-orbertable bromomethylthiophene-2-carbonitrile (3.23 g. 16 mmol) and sodium hydride (60%) (0.67 g, 16.8 mmol). After addition, the solution is allowed to warm to

ambient temperatures. After 2 hours, the solution is quenched by the addition of sat NH,Cl. The solution is diluted with H₂O and EtOAce The layers are separated. The organic layer is washed with H2O and sat. NaCl. The organic layer is dried over MgSO₄, filtered and concentrated. The crude product is purified by column chromatography eluting with gradient of 20% EtOAc/CH2Cl2 to 30% EtOAc/CH₂Cl₂ to afford the title compound (4 g, 13.8 mmol) as a white solid. ¹H NMR (CDCI₃, 300 MHz) δ 7.51 (s, 1H), 7.45 (s, 1H), 5.12 (bs, 1H), 4.42 (AB, 2H), 4.12 (m, 1H), 3.27 (m, 2H), 2.58 (m, 1H), 1.93 (m, 1H), 1.42 (s, 9H),

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einter ichnockene eintvitteliggisere 2-carbinite G. 4-(3-Amino-2-oxopyrrolidine-1-ylmethyl)thiophene-2-carbonitrile hydrochloride 280 enidoros - ynerigin to also di 1947 to Din 083 [1-(5-Cyanothiophene-3-ylmethyl)-2-oxopyrrolidin-3-yl]carbamic acid tert-butyl ester (4 g, 13.8 mmol) is added to a solution of 100 mL of EtOAc sat. with HCl gas at 0°C. After 3 hours, the solution is concentrated. The title compound (3.3 g, 13.5 mmol) is obtained as a white solid. nifer stew sits (fema)

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 1 H NMR (DMSO-d₆, 300 MHz) δ 8.61 (bs, 3H), 7.96 (s, 1H), 7.82 (s, 1H), 5.12 (bs, 1H), 4.42 (AB, 2H), 4.00 (m, 1H), 3.27 (m, 2H), 2.31 (m, 1H), 2.03 (m, 1H).

EXAMPLE 123

5 <u>5-(3-Amino-2-oxopyrrolidine-1-ylmethyl)thiophene-2-carbonitrile hydrochloride</u>

A. (5-Bromothiophene-2-yl)methanol.

To a solution of 5-bromothiophene-2-carboxaldehyde (15 g, 79 mmol) in 250 mL of THF is added NaBH₄ (3 g, 86 mmol). After 1hour, the reaction is quenched by the addition of 100 mL of sat. NH₄Cl. The resulting solution is diluted with Et₂O. The layers are separated. The organic layer is washed with H₂O and sat. NaCl. The organic layer is dried over MgSO₄, filtered and concentrated. The crude product is purified by column chromatography eluting with gradient of 5% EtOAc/ hexanes to 10% EtOAc/hexanes to afford the title compound (13.7 g, 71 mmol) as an oil.

14 NMR (CDCl₃, 300 MHz) δ 6.91 (d, 1H), 6.74 (d, 1H), 4.72 (s, 2H), 2.16 (bs, 1H).

B. 5-Hydroxymethylthiophene-2-carbonitrile.

- The title compound is prepared as described in EXAMPLE 122, Part C using (5-bromothiophene-2-yl)methanol as the starting material. The crude product is purified by column chromatography eluting with gradient of 20% EtOAc/hexanes to 30% EtOAc/hexanes to afford the title compound as a clear oil.
- ¹H NMR (CDCl₃, 300 MHz) δ 7.52 (d, 1H), 6.97 (d, 1H), 4.87 (s, 2H), 2.26 (bs, 1H).

C. 5-Bromomethylthiophene-2-carbonitrile.

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The title compound is prepared as described in EXAMPLE 122, Part D using 5-hydroxymethylthiophene-2-carbonitrile as the starting material. The crude product is purified by column chromatography eluting with gradient of 10% EtOAc/hexanes to 20% EtOAc/hexanes to afford the title compound as a white solid.

 1 H NMR (CDCl₃, 300 MHz) δ 7.49 (d, 1H), 7.09 (d, 1H), 4.66 (s, 2H).

D. [1-(5-Cyanothiophene-2-ylmethyl)-2-oxopyrrolidin-3-yl]carbamic acid tert-butyl ester.

The title compound is prepared as described in EXAMPLE 122, Part F using 5-bromomethylthiophene-2-carbonitrile in place of 4-bromomethylthiophene-2-carbonitrile. The crude product is purified by column chromatography eluting with gradient of 10% EtOAc/CH₂Cl₂ to 30% EtOAc/ CH₂Cl₂ to afford the title compound as a white solid.

¹H NMR (CDCl₃, 300 MHz) δ 7.51 (d, 1H), 6.98 (d, 1H), 5.09 (bs, 1H), 4.64 (AB, 2H), 4.17 (m, 1H), 3.30 (m, 2H), 2.62 (m, 1H), 1.93 (m, 1H), 1.43 (s, 9H).

E. 5-(3-Amino-2-oxopyrrolidine-1-ylmethyl)thiophene-2-carbonitrile

10 <u>hydrochloride</u>

The title compound is prepared as described in EXAMPLE 122, Part G using [1-(5-cyanothiophene-2-ylmethyl)-2-oxopyrrolidin-3-yl]carbamic acid tert-butyl ester as the starting material. The title compound is obtained as a white solid.

¹H NMR (DMSO-d₆, 300 MHz) δ 8.59 (bs, 3H), 7.90 (d, 1H), 7.62 (d, 1H), 5.10

15 (bs, 1H), 4.63 (AB, 2H), 4.10 (m, 1H), 3.25 (m, 2H), 2.28 (m, 1H), 2.05 (m, 1H).

EXAMPLE 124

5-(3-Amino-2-oxopyrrolidine-1-ylmethyl)thiophene-3-carbonitrile hydrochloride

20 A. (4-Bromothiophene-2-yl)methanol.

The title compound is prepared as described in EXAMPLE 123, Part A using 4-bromothiophene-2-carboxaldehyde as the starting material. The title compound is obtained as a clear oil.

EI MS, [M] *= 192.

25

B. 5-Hydroxymethylthlophene-3-carbonitrile.

The title compound is prepared as described in EXAMPLE 122, Part C using (5-bromothiophene-2-yl)methanol as the starting material. The crude product is purified by column chromatography eluting with gradient of 20%

30 EtOAc/hexanes to 40% EtOAc/hexanes to afford the title compound as a clear oil.

¹H NMR (CDCl₃, 300 MHz) δ 7.83 (s, 1H), 7.12 (s, 1H), 4.80 (AB, 2H), 2.27 (bs, 1H). EI MS, [M]⁺=139.

35 C. 5-Bromomethylthiophene-3-carbonitrile.

The title compound is prepared as described in EXAMPLE 122, Part D using

5-hydroxymethylthiophene-3-carbonitrile as the starting material. The crude product is purified by column chromatography eluting with gradient of 5% EtOAc/ hexanes to 15% EtOAc/ hexanes to afford the title compound as a white solid.

 1 H NMR (CDCl₃, 300 MHz) δ 7.91 (d, 1H), 7.27 (d, 1H), 4.65 (s, 2H).

D.: [1-(4-Cyanothiophene-2-ylmethyl)-2-oxopyrrolidin-3-yl]carbamic acid tertabutyl ester. Fig. 50.0000 acades a carbon parameter of the control of the contr

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The title compound is prepared as described in EXAMPLE 122, Part F using 5-bromomethylthiophene-3-carbonitrile in place of 4-bromomethylthiophene-2-carbonitrile. The crude product is purified by column chromatography eluting with gradient of 20% EtOAc/CH₂Cl₂ to 40% EtOAc/ CH₂Cl₂ to afford the title compound as a white solidable and the compound and the compound as a white solidable and the compound as a white solidable and the compound as a white solidable and the compound and the compound as a white solidable an

¹H NMR (CDCl₃, 300 MHz) δ 7.86 (s, 1H), 7.14 (s, 1H), 5.09 (bs, 1H), 4.62 (AB, 15 2H), 4.16 (m, 1H), 3.30 (m, 2H), 2.62 (m, 1H), 1.90 (m, 1H), 1.42 (s, 9H).

E. 5-(3-Amino-2-oxopyrrolldine-1-ylmethyl)thiophene-3-carbonitrile hydrochloride

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The title compound is prepared as described in EXAMPLE 122, Part G using [1-(4-cyanothiophene-2-ylmethyl)-2-oxopyrrolldin-3-yl]carbamic acid tert-butyl ester as the starting material. The title compound is obtained as a white solid. [H NMR (CDCl₃:300 MHz) δ 8.72 (bs, 3H), 7.81 (s, 1H), 7.35 (s, 1H), 5.10 (bs, 1H); 4.63 (AB, 2H); 4.40 (m, 1H); 3.38 (m, 2H); 2.62 (m, 1H), 2.50 (m, 1H).

25 EXAMPLE: 125be. are dec ene cieve. Ent i.O.H this nAO.B this before the case of a cieve. Ent i.O.H this nAO.B this before the case of a cieve. Ent i.O.H this nAO.B this before the case of the cas

A: 7-Methoxynaphthalene-2-sulfonic acid. sodium salt.

column of contraction approximation gradient of 10% EIOAc/ CH₂OI₂ to for a

To a suspension of 7-hydroxynaphthalene-2-sulfonic acid, sodium salt (10 g, 40.2 mmol) in 150 ml2 of 2:1 H₂O/ethanol is added solid NaOH (1.79 g, 44.7 mmol) at room temperature. The mixture is stirred until a homogenous solution forms, and dimethyl sulfate (4.23 mL, 44.7 mmol) is then added. A precipitate eventually forms and the mixture is stirred over a period of 16 hours. The crude mixture is concentrated in vacuo and the residue is stirred in 100 mL of

The residue is concentrated in vacuo and the residue is stirred in 100 mL of the concentrated in vacuo and the residue is stirred in 100 mL of the concentrated in 100 mL of the concentra

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solid is heated at reflux in 100 mL of 95% EtOH for 2 hours, allowed to cool to
    room temperature, filtered and dried to give 8.12 g of the title compound.
1H NMH (DMSO<sub>3</sub>d<sub>e</sub>, 300 MHz) δ,8.07 (s;1H), 7.78 (m;2H), 7.54 (dd, 1H), 7.38
          (s, 1H), 7.14 (dd, 1H), 3.86 (s, 3H)
```

1H NMH (CDC), 200 MHz) 8 7.91 (d, 114), 7.27 (d, 114), 4 65 (s, 214). B. 7-Methoxynaphthalene-2-sulfonyl chloride.

A mixture of 7-methoxynaphthalene-2-sulfonic acid/sodium salt (8:12 g, 31.1 mmol) in 80 mL of thionyl chloride is heated at 80°C for 3 hours. Affew drops of DMF is added with vigorous bubbling resulting and the mixture is heated for an additional 1.5 hours. The mixture is allowed to cool to room temperature and concentrated in vacuo. The residue is diluted in EtOAc and washed successively with water (2x); 1 N HCl solution and saturated NaClivThe organic layer is dried over anhydrous MgSO45 filtered and concentrated. The crude product is purified by column chromatography eluting with 20% EtOAc/hexanes to afford the title compound (5:2 g, 20.2 mmol) as a white solid. 1H NMR (CDCl₃, 300 MHz) d 8.49 (d, 1H), 7.96 (d, 1H), 7.85 (d, 2H), 7.39 (dd, 1H),,7,29 (d,,1H),,3,99 (s, 3H),,EI MS, [M]T=2565xc-\$50000A-81-8 (d)

hydroch ande

7-Methoxynaphthalene-2-sulfonic acid-[1-(5-cyanothiophen-3-ylmethyl)-2-Oxopyrrolidin-3-(S)-ylamide. 2-oxo-2-ylmethyl-2-oxo-2-ylmethyl-2-oxo-3-ylmethyl-3-oxo-3-ylmethyl-2-oxo-3-ylmethyl-2-oxo-3-ylmethyl-2-oxo-3-ylmethyl-2-oxo-3-ylmethyl-3-oxo-3-ylmethyl-3-oxo-3-ylmethyl-3-oxo-3-ylmethyl-3-oxo-3-ylmethyl-3-ylmethyl-3-oxo-3-ylmethyl-3-oxo-3-ylmethyl-3-oxo-3-ylmethyl-3-oxo-3-ylmethyl-3-oxo-3-ylmethyl-3-To a solution of 4-(3-Amino-2-oxopyrrolidine-1-ylmethyl)thiophene-2carbonitrile hydrochloride (0.43 g. 1.8 mmol), prepared as in EXAMPLE 122, in 10 mL of CH2Cl2 is added 7-methoxynaphthalene-2; sulfonyl chloride (0.51 g. 2 mmol) and triethyl amine (0.55 g, 5.4 mmol). After 16 hours, the solution is diluted with EtOAc and H₂O. The layers are separatedasThe organic layer is 25 washed with 1 N HCl. sat. NaHCO and sat. NaCl. The organic layer is dried over MgSO4, filtered and concentrated. The crude product is purified by column chromatography eluting with gradient of 10% EtOAc/ CH2Cl2 to 20% EtOAc/CH₂Cl₂ to afford the title compound (0.50 g):1.22 mmol) as a white solid. ¹H NMR (CDCI₃, 300 MHz) δ 8.32 (s. 1H), 7.90 (d. 1H), 7.82 (d. 1H), 7.73 (dd, 30 1H), 7.42, (s., 1H), 7.36 (s, 1H), 7.30 (dd, 1H), 7.26 (m, 1H), 5.33 (bs; 1H), 4.29 (AB, 2H), 3.95 (s, 3H), 3.70 (m, 1H), 3.22 (m, 2H), 2.61 (m, 1H), 2.08 (m, 1H). Solution

forms, and dimethyl suifate (4.28 mt., 44 7 mmot) is then,)-(7-Methoxynaphthalene-2-sulfonylamino)-2-oxopyrrolidin-1vlmethyl]thiophene-2-carboxamidine trifluoroacetate: פונים בו פונים אונים וויים בו פונים בו פונים וויים בו פונים בו פונים וויים בו פונים בו To a solution of 7-methoxynaphthalene-2-sulfonic acid-[1-(5-cyanothiophen-3ylmethyl)-2-oxopyrrolidin-3-(S)-yl]amide (0.3 g, 0.73 mmol) in 20 ml of

- EtOAc:CH₂Cl₂ (2:1) at 0°C is bubbled HC gas for 5 minutes. After 5 hours, the solution is concentrated. The resulting residue is dissolved in 20 mL of MeOH and cooled to 0°C. Ammonia gas is bubbled into the solution for 5 minutes. After this time the solution is heated to 50°C for 3 hours. The
- solution is then concentrated. The resulting crude material is purified by RP-HPLC eluting with a gradient of 10% CH₃CN/H₂O (0.1% TFA) to 60% CH₃CN/H₂O (0.1% TFA) and the appropriate product fractions are lyophilized to provide the title compound (0.13 g, 0.23 mmol) as a white solid.

 1H NMR (DMSO-d₆, 300 MHz) δ 9.26 (bs, 2H), 9.07 (bs, 2H), 8.33 (bs,1H), 8.16
- 10 (d,1H), 7.98 (d, 1H), 7.91 (d, 1H), 7.82 (s, 1H), 7.69 (dd, 1H), 7.53 (s, 1H), 7.30 (dd, 1H), 4.31 (AB, 2H), 4.08 (m, 1H), 3.87 (s, 3H), 3.06 (m, 2H), 3.06 (m, 2H), 1.95 (m, 1H), 1.55. FAB MS, [M+H] = 458. Elemental analysis calculated with 1 mmol of H₂O and 1.5 mmol of excess TFA cal. C=45.64%, H=4.07%, N=8.87%, found C=45.88%, H=3.97%, N=9.12%.
- EXAMPLE-126 the respective to the product of the pr
- A. 7-Methoxynaphthalene-2-sulfonic acid-[1-(5-cyanothiophen-3-ylmethyl)-2-oxopyrrolidin-3-(S)-yllmethylamide.

 To a solution of 7-methoxynaphthalene-2-sulfonic acid-[1-(5-cyanothiophen-3-ylmethyl)-2-oxopyrrolidin-3-(S)-yl]amide (2.36 g, 5.35 mmol), prepared as in EXAMPLE 125, Part C, in 16 mL of DMF is added MeI (1.14 g, 8.03 mmol) and
- 25 K₂CO₃ (1.11 g, 8.03 mmol). After 16 hours, the solution is diluted with EtOAc and H₂O. The layers are separated of the organic layer is dried over MgSO₄, filtered and concentrated.
- (2)The crude product is purified by column chromatography eluting with gracient of 5% EtOAc/CH₂Cl₂ to 15% EtOAc/CH₂Cl₂ to afford the title compound (2.30 g, 30 5.05 mmol) as a white solid. The last policy of the little compound (2.30 g, 14 NMR (CDC) 200 MMR (2.30 g), 15 NMR (2.30 g), 15 N
- ¹H NMB (CDCl₃, 300 MHz) δ 8.40 (s. 1H), 7.91 (d, 1H), 7.82 (s. 1H), 7.78 (s. 1H), 7.46 (s. 1H), 7.39 (s. 1H), 7.27 (m, 2H), 4.88 (t. 1H), 4.40 (AB, 2H), 3.95 (s. 3H), 3.26 (m, 2H), 2.80 (s. 3H), 2.38 (m, 1H), 2.05 (m, 1H). (a) 0.6.7 (c) (a) 0.6.7 (c) (a) 0.6.7 (c) (b) 0.6.7 (c) (c) 0.6.7 (c) 0.6.7

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35 B. 4-(3-(S)-[(7-Methoxynaphthalene-2-sulfonyl)methylamino]-2-oxopyrrolidin-1-ylmethyl)thiophene-2-carboxamidine-trifluoroacetate.

and selection acid-[1-(5-cyanothiophen-3-ylmethyl)-2-High the gxopyrrolidin-3-(S)-yl]methylamide is converted to the title compound as described in EXAMPLE 125; Part D. The crude product is purified by RP-HPLC and eluting in a gradient of 10% CH₂CN/H₂O (0.1%) TFA) to 80% CH₂CN/H₂O (0.1%) 5. TFA) and the appropriate product fractions are lyophilized to provide the title FP-4PLC suring with a gradient of 10% bilospathwa as a bnuogmostენ ერეში ერე ერე (ტოვი ექ_ა, 300 <u>ტოკ</u>ი გ. გ. 24 (ხაუ2H), 8:97მ (ხაე2H), 8:39 (s, 1H), 8.02 (d,1H),7.95 (d, 1H),7.91 (s, 1H),7.80 (s, 1H),7.68 (dd, 1H), 7.55 (s, 1H), 7.32 (ht (dd, 1H), 4.86 (t, 1H), 4.37 (AB, 2H), 3.87 (s, 3H), 3.46 (m, 1H), 3.14 (m, 1H). . 10_{(H1}2,46₂(s, 3H), 1,95 (m, 1H), 1,74 (m, 1H). FAB MS, [M+H] = 473. Elemental f (HS m) analysis calculated with 1,5 mmol of H2O cals C=46.98%, H=4.60%; N=9.13%. found C=46.86%, H=3.97%, N=4.29%; OM BAH .cd.r. (Int. an) 78 2 1 - mov 3/14,0 and 1.5 mnol of excess TFA ca. C=45.54%, H=4.07%, H=0.07%, H=0.07%, N=0.10%, N=0.10%, H=1.07%, N=0.10%, N N=5.67% found C=45.88%, H=3.97%, N=9.12%. 15 2-[[1-(5-Carbamimidovlthiophene-3-vlmethyl)-2-oxopyrrolidin-3-(S)-vl1(7-2) methoxynaphthalene-2-sulfonyl)aminolacetamide trifluoroacetate. e-(3-(3)-f(Z-Methoxynaphthalene-2-sulftanthylaminot-2-oxopy rolldin A. 2-[[1-(5-Cyanothiophene-3-vlmethyl)-2-oxopyrrolidin-3-(S)-vl1(7methoxynaphthalene-2-sulfonyl)aminolacetic acid tert-butyl ester. 20, The title compound is prepared as in EXAMPLE 126, Part A using tert-butylbromoacetate in place of Mel to give the title compound as a white foam. 1H NMR (CDCl₃, 300 MHz) δ 8.42 (s, 1H), 7.78 (m, 3H), 7.48 (s, 1H), 7.39 (s, 1H), 7.25 (m, 2H), 4.52 (t, 1H), 4:40 (AB, 2H); 4:22 (AB, 2H), 3:95 (S, 3H), 3.26 以OO。(1.11 g. 8:03 mmcl) After (6 hours, the solution is diluted with いつ B. 2-[[1-(5-Cyanothiophene-3-ylmethyl)-2-oxopyrrolidin-3-(\$)-vi](7-5-13methoxynaphthalene-2-sulfonyl)aminolacetic acid approvail # #JasV JasV To a solution of 2-[[1-(5-cyanothiophene-3-ylmethyl)-2-oxopyrrolidin-3-(S)-yl]-(7-methoxynaphthalene-2-sulfonyl)amino]acetic acid tert-butyl ester (0.40 g, 0.72 mmol) in 15 mL of CH₂Cl₂ is added 5 mL of TFA. After 2 hours the solution is concentrated to give the title compound as a white foam Will ¹H NMR (CDCI₃, 300 MHz) δ 8.36 (s, 1H); 7.91 (d, 1H); 7:80 (d, 1H), 7.68 (d, 1H), 7.50 (s, 2H), 7.31 (m. 1H), 7.25 (m. 1H), 7.14 (m. 1H), 4.73 (f. 1H), 4.47 (s, 2H), 3.95 (s, 3H), 3.92 (AB, 2H), 3.32 (m, 2H), 2.42 (m, 1H), 2.13 (m, 1H). methoxynaphthalene-2-sulfonyl)aminolacetamide.

To a solution of 2-[[1-(5-cyanothiophene-3-ylmethyl)-2-oxopyrrolidin-3-(S)-yl]-(7-methoxynaphthalene-2-sulfonyl)amino]acetic acid (0.40 g, 0.80 mmol) in 6 mL of THF at -15°C is added triethyl amine (0.10 g, 0.96 mmol) and ethyl chloroformate (0.09 g, 0.84 mmol). The solution is stirred for 1 hour. After this time, NH₄OH (0.07 mL, 0.90 mmol) is added and the solution is allowed to warm to ambient temperatures. After 16 hours, the solution is diluted with EtOAc. The solution is washed with 1 N HCl, sat. NaHCO₃ and sat. NaCi. The organic layer is dried over MgSO₄, filtered and concentrated. The title compound (0.28 g, 0.56 mmol) is obtained as a white foam.

10 ... H NMR (CDCl₃, 300 MHz) δ 8.38 (s, 1H), 7.88 (m, 3H), 7.38 (m, 4H), 4.51 (AB, 2H), 4.12 (m, 1H), 3.95 (s, 3H), 3.78 (AB, 2H), 3.26 (m, 2H), 2.32 (m, 2H).

D. 2-[[1=(5-Carbamimidoy(thiophene-3-ylmethyl)-2-oxopyrrolidin-3-(S)-yl](7-methoxynaphthalene-2-sulfonyl)amino]acetamide trifluoroacetate.

- 2-[[1-(5-Cyanothiophene-3-ylmethyl)-2-oxopyrrolidin-3-(S)-yl]-(7-methoxynaphthalene-2-sulfonyl)amino]acetamide is converted to the title compound as described in EXAMPLE 125, Part D. The crude product is purified by RP-HPLC eluting in a gradient of 10% CH₃CN/H₂O (0.1% TFA) to 60% CH₃CN/H₂O (0.1% TFA) and the appropriate product fractions are
- lyophilized to provide the title compound as a white solid.

 ¹H NMR (DMSO-d₆, 300 MHz) δ 9.23 (bs, 2H), 8.91 (bs, 2H), 8.41 (s, 1H), 7.92 (m, 3H), 7.78 (m, 2H), 7.58 (m, 2H), 7.32 (dd, 1H), 7.20 (m, 1H), 4.78 (t, 1H), 4.38 (AB, 2H), 3.90 (s, 3H), 3.67 (AB, 12H), 3.18 (m, 2H), 2.04 (m, 2H). FAB MS, [M+H] *=516.

1 / m. 28 / gH) / 9 3 / S (FIR a) / T 1 / 4 / 4 / 4 / 4 / 6 / 6 / 6 / 6 / 5 / 5

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EXAMPLE 128

4-(3-(S)-[(7-Methoxynaphthalene-2-sulfonyl)benzylaminol-2-oxopyrrolidin-1-ylmethyl}thiophene-2-carboxamidine trifluoroacetate.

A. 7-Methoxynaphthalene-2-sulfonic acid-[1-(5-cyanothiophen-3-ylmethyl)-2

oxopyrrollidin-3-(S)-yllbenzylamide.

The title compound is prepared as in EXAMPLE 126, Part A using her...!

bromide in place of Mel to give the title compound as a white foam.

¹H NMR (CDCl₃, 300 MHz) δ 8.44 (s, 1H), 8.00 (s, 1H), 7.91 (m, 1H), 7.79 (d, 1H), 7.53 (d, 1H), 7.23 (m, 8H) 4.52 (m, 3H), 4.36 (AB, 2H), 3.95 (s, 3H), 3.08

(dd, 2H), 2:28 (m, 4H), 2:05 (m, 1H); (fit (元) 3) (fit

4-{3-(S)-[(7-Methoxynaphthalene-2-sulfonyl)benzylamino]-2-oxo-pyrrolidin-1-ylmethyl)thiophene-2-carboxamidine trifluoroacetate: ryxontern Xy 7-Methoxynaphthalene-2-sulfonic acid-[1-(5-cyanothiophen-3-ylmethyl)-2oxopyrrolidin-3-(S)-yl]-benzylamide is converted to the title compound as described in EXAMPLE 125, Part D. The crude product is purified by RP-HPLC eluting in a gradient of 10% CH₃CN/H₂O₃(0.1%,TFA) to 80% CH₃CN/H₂O₃(0.1% TFA) and the appropriate product fractions are lyophilized to provide the title compound as a white solid. อาสา การประการ เคาะสาร์เการประการสาร์เการประการสาร์เการ ¹H NMR (DMSO-d₆, 300 MHz) δ 9.22 (bs, 2H), 9.08 (bs, 2H), 8.41 (s, 1H), 8.00 10, (d,1H), 7.96 (d,1H), 7.87 (s,(1H), 7.80 (m, 2H); 7.52 (s;(1H)) 7.21 (m, 6H); 4.71 (t, 1H), 4.40 (AB, 2H), 4.24 (AB, 2H), 3.88 (s, 3H), 3.11 (m, 1H), 2.93 (m, 1H), 2.12 (m, 1H), 1.62 (m, 1H). FAB MS, [M+H] += 549. Elemental analysis cal. C=54.37%, H=4.41%, N=8.45%, found, C=53.80%, H=4.45%, N=8.11% co.hoxvnaphinalene-2-sullenvi eminoladets 15 2-[[1-(5-Cyanothiophene-2-vimetty 3-2-expoyredidin-4-[3-(S)-(5-Chloro-3-methylbenzo[b]thiophene-2-sulfonvlamino)-2-oxopyrrolidin-1-ylmethyl]thiophene-2-carboxamidine trifluoroacetate.nep purilled by RF HPLO eluting in engadiant of 10% CH, CNALO (0.1%, TYA) in A. 5-Chloro-3-methylbenzo[b]thiophene -2-sulfonic acid-[1-(5-cvanothiophen-3-ylmethyl)-2-oxopyrrolidin-3-(S)-yllamide: erh elevora or best adqovl 20 The title compound is prepared as in EXAMPLE 125; Part C using 5-chloro-3methylbenzo[b]thiophene -2-sulfonyl chloride in place of 7-methoxy-(Fi) naphthalene-2-sulfonyl chloride to give the title compound as a white foam. 3/17 H NMR (CDCl₃, 300 MHz) δ 7.89 (m, 2H), 7.43 (m, 3H), 5.69 (bs, 1H), 4.42 (s, 2H), 3.90 (m, 1H), 3.26 (m, 2H), 2.70 (s, 3H), 2.62 (m, 1H), 1.89 (m, 1H). 25 EXAMPLE 128 B. 4-[3-(S)-(5-Chloro-3-methylbenzo[b]thiophene-2-sulfonylamino)-2oxopyrrolidin-1-ylmethylj-thiophene-2-carboxamidine trifluoroacetate. 5-Chloro-3-methylbenzo[b]thiophene-2-sulfonic acid-[1-(5-cyanothiophen-3ylmethyl)-2-oxopyrrolidin-3-(S)-yl]amide is converted to the title compound as 30 described in EXAMPLE 125, Part D. The crude product is purified by RP-HPLC eluting in a gradient of 10% CH₃CN/H₂O (0.1% TFA) to 60% CH₃CN/H₂O (0.1% TFA) and the appropriate product fractions are lyophilized to provide the title compound as a white solid. (CHI) PAR 8 (CHM 008 (COCT) HOW H H NMR (DMSO-d_s, 300 MHz) δ 9.21 (bs., 2H), 8.87 (bs., 2H), 8.69 (d,1H), 9.04 (m,2H), 7.80 (m, 2H), 7.54 (d, 1H), 4.31 (AB, 2H), 4.12 (m, 1H), 3.11 (m, 2H),

2.58 (s, 3H), 2.03 (m, 1H), 1.60 (m, 1H). FAB MS, [M+H] +=483.

EXAMPLE 130

5-{3-(S)-[(7-Methoxynaphthalene-2-sulfonyl)methylamino]-2-oxopyrrolidin-1-ylmethyl}thiophene-3-carboxamidine trifluoroacetate.

A. 7-Methoxynaphthalene-2-sulfonic acid [1-(4-cyanothiophen-2-ylmethyl)-2-oxopyrrolidin-3-(S)-yllamide.

The title compound is prepared as in EXAMPLE 125, Part C using 5-(3-amino-2-oxopyrrolidine-1-ylmethyl)thiophene-3-carbonitrile hydrochloride, prepared as in EXAMPLE 124, in place of 4-(3-amino-2-oxopyrrolidine-1-ylmethyl)-thiophene-2-carbonitrile hydrochloride. The crude product is purified by column chromatography eluting with gradient of 10% EtOAc/CH₂Cl₂ to 20% EtOAc/ CH₂Cl₂ to afford the title compound as a white solid.

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B. 7-Methoxynaphthalene-2-sulfonic acid [1-(4-cyanothiophen-2-ylmethyl)-2-oxopyrrolidin-3-(S)-yl]methylamide.

The title compound is prepared as in EXAMPLE 126, Part A using 7-methoxynaphthalene-2-sulfonic acid [1-(4-cyanothiophen-2-ylmethyl)-2-

- oxopyrrolidin-3-(S)-yl]amide in place of 7-methoxynaphthalene-2-sulfonic acid [1-(5-cyanothiophen-3-ylmethyl)-2-oxopyrrolidin-3-(S)-yl]amide. The crude product is purified by column chromatography eluting with gradient of 5% EtOAc/CH₂Cl₂ to 15% EtOAc/CH₂Cl₂ to afford the title compound as a white solid.
- 25 ¹H NMR (CDCl₃, 300 MHz) δ 8.41 (s, 1H), 8.00 (m, 1H), 7.90 (d, 1H), 7.82 (s, 1H), 7.76 (m, 2H), 7.24 (m, 2H), 7.10 (s, 1H), 4.92 (t, 1H), 4.58 (AB, 2H), 3.91 (s, 3H), 3.29 (m, 2H), 2.73 (s, 3H), 2.37 (m, 1H), 2.03 (m, 1H), 2.03 (m, 2H), 2.73 (s, 3H), 2.37 (m, 1H), 2.03 (m, 2H), 2.73 (s, 3H), 2.37 (m, 1H), 2.03 (m, 2H), 2.73 (s, 3H), 2.37 (m, 1H), 2.03 (m, 2H), 2.73 (s, 3H), 2.37 (m, 1H), 2.03 (m, 2H), 2.73 (s, 3H), 2.37 (m, 1H), 2.03 (m, 2H), 2.73 (s, 3H), 2.37 (m, 1H), 2.03 (m, 2H), 2.73 (s, 3H), 2.37 (m, 1H), 2.03 (m, 2H), 2.73 (s, 3H), 2.37 (m, 1H), 2.03 (m, 2H), 2.73 (s, 3H), 2.37 (m, 1H), 2.03 (m, 2H), 2.73 (s, 3H), 2.37 (m, 1H), 2.03 (m, 2H), 2.73 (s, 3H), 2.37 (m, 1H), 2.03 (m, 2H), 2.73 (s, 3H), 2.37 (m, 1H), 2.03 (m, 2H), 2.73 (s, 3H), 2.37 (m, 1H), 2.03 (m, 2H), 2.73 (s, 3H), 2.37 (m, 1H), 2.03 (m, 2H), 2.73 (s, 3H), 2.37 (m, 1H), 2.03 (m, 2H), 2.73 (s, 3H), 2.37 (m, 1H), 2.03 (m, 2H), 2.73 (s, 3H), 2.37 (m, 2H), 2.73 (m,

C.::5-{3-(S)-[(7-Methoxynaphthalene-2-sulfonyl)methylamino]-2-oxopyrrolidin-30 <u>1-ylmethyl}thiophene-3-carboxamidine hvdrochloride beathylamino</u>

oxopyrrolidin-3-(S)-yl]-methylamide is converted to the title compound as described in EXAMPLE 125, Part D. The crude product is purified by RP-HPLC eluting in a gradient of 10% CH₂CN/H₂O to 80% CH₂CN/H₂O and the

35 (Happropriate product fractions are lyophilized to provide the title compound as a

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¹H NMR (DMSO-d_s, 300 MHz) δ 8.88 (bs, 4H), 8.41 (s,1H), 8.35 (s,1H), 8.00 (d, 1H), 7.92 (d, 1H), 7.68 (dd, 1H), 7.57 (s, 1H), 7.48 (s, 1H), 7.32 (dd, 1H), 4.82 (t, 1H), 4.50 (AB, 2H); 3.88 (s, 3H), 3.21 (m, 2H); 2.63 (s; 3H), 2.00 (m, 4H), 1.72 (m, 1H). FAB MS, [M+H] = 473. Elemental analysis calculated with 0.75 mmol of H₂O cal. C=50.57%, H=5.11%, N=10.72%, Cl=6.78%, found C=50.52%, 2 Tyritan H=4.96%; N=10.46%, Cl=6.91%; when a sense and decremental A 2x2D/mol/Co.11(S)-vilon/Gxc

The title contactind is prepared as it, EXAMPLE (25 16), 319 MAXA, (3-pm) . . .

13-16Ge 10 4-(3-(S)-[(-5-Chloro-3-methylbenzo[b]thiophene-2-sulfonyl)benzylamino]-2-

10 oxopyrrolidin-1-ylmethyl}thiophene-2-carboxamidine trifluoroacetate. thiophene-2-carbonitrile hydrochloride. The crude groduct is purlied by

A. 5-Chloro-3-methylbenzo[b]thiophenel-2-sulfonic acid [1-(5-cyanothiophen-3-ylmethyl)-2-oxopyrrolidin-3-(S)-yl]-benzylamides വ ്ലീറ്റ് HO പ്രവിദ The title compound is prepared as in EXAMPLE 126. Part A using 5-chloro-3-

methylbenzo[b]thiophene-2-sulfonic acid [1-(5-cyanothiophen-3-ylmethyl)-2-S-1/1/18 Oxopyrrolidin-3-(S)-yllamide, prepared as in EXAMPLE 129 Part A. in place of 7-methoxynaphthalene-2-sulfonic acid [1-(5-cyanothiophen-3-ylmethyl)-2oxopyrrolidin-3-(\$)-yl]amide and benzyl bromide in place of Mel. The crude

c product is purified by column chromatography eluting with gradient of 40% 20 of EtOAc/ hexanes to 50% EtOAc/hexanes to afford the title compound as a white

Plants solid, editorally (8)-6-obitomosys S-flythed N. 8-radiolitionary Ph. D. 7.32 (m, 2H), 7.32 (m, 2H), 7.28 (m, 2H), 4.88 (AB, 1H), 4.64 (t, 1H), 4.38 (AB, 2H), 4.22 (AB, 1H), 3.06 (m, 1H), 2.90 (m, 1H), 2.71 (s, 3H), 2.28 (m, 1H), 1.81 (m. 1H). 25 - HAMP (1900), 300 MHz, & 341 (a), 1-1), 830 (m, 1H), 7.90 (3, 1H), 7.20 **25**

B. 4-(3-(S)-[(5-Chloro-3-methylbenzo[b]thiophene-2-sulfonyl)benzylamino]-2oxopyrrolidin-1-ylmethyl}thiophene-2-carboxamidine trifluoroacetate-5-Chloro-3-methylbenzo[b]thiophene-2-sulfonic acid [1-(5-cyanothiophen-3ylmethyl)-2-oxopyrrolidin-3-(S)-yl]benzylamide is converted to the title

compound as described in EXAMPLE,125, Part DroThe crude product is OS purified by RR-HPLC eluting in a gradient of 10% CH, CN/H;O (0.1% TFA) to 80%, CH3CN/H2O1(0.1% TFA) and the appropriate product fractions are ்து நெlyophilized to provide the title compound as a white solid? எ badhoses 'H NMR (DMSO-d_{e:}300 MHz) δ 9.30 (bs, 2H); 9.25 (bs; 2H), 8.05 (s; 1H), 8.03

35 (s,1H), 7,82 (s, 1H), 7.80 (s, 1H), 7.55 (dd, 1H), 7.28 (m, 2H), 7.21 (m, 3H), 4.82 (t, 1H), 4.62 (AB, 1H), 4.25 (AB, 2H), 4.20 (AB, 1H), 3.13 (m, 1H), 2.91 (m, 1H), 2.60 (s, 3H), 2.15 (m, 1H), 1.62 (m, 1H). FAB MS, [M+H]+=573. Elemental

)

analysis cal. C=48.94%, H=3.81%, N=8.15%, found C=48.60%, H=3.71%, N=7.90%.

EXAMPLE 132

- 5 4-{3-(S)-[(Methanesulfonyl)-(3-phenylpropyl)amino]-2-oxopyrrolidin-1-ylmethyl}thiophene-2-carboxamidine trifluoroacetate.
- A. Methanesulfonic acid [1-(5-cyanothiophen-3-ylmethyl)-2-oxopyrrolldin-3-(S)-yl]amide.
- The title compound is prepared as in EXAMPLE 125, Part C using methane sulfonyl chloride in place of 7-methoxynaphthalene-2-sulfonyl chloride to give the title compound as a white foam.
- 2H), 4.18 (m, 1H), 3.39 (m, 2H), 3.15 (s, 3H), 2.60 (m, 1H), 2.00 (m, 1H).
- B. Methánesulfonic acid [1-(5-cyanothiophen-3-ylmethyl)-2-oxopyrrolidin-3-(S)-yl]-(3-phenylpropyl)amide?

The title compound is prepared as in EXAMPLE 126, Part A using methanesulfonic acid [1-(5-cyanothiophen-3-ylmethyl)-2-oxopyrrolidin-3-(S)-

- yl]amide in place of 7-methoxynaphthalene-2-sulfonic acid [1-(5-cyano-thiophen-3-ylmethyl)-2-oxopyrrolidin-3-(S)-yl]amide and phenethyl bromide in place of MeI to give the title compound as a white foam.
- 25 or (m, 2H), 1:94 (m, 2H). Textended as a wine loan.

 26 or post H-NMR (CDC); 300 MHz) & 7.48 (s; 1H), 7.40 (s, 1H), 7.23 (m, 5H), 4.52 (AB, 1H); 3.22 (m, 4H); 3.12 (s, 3H), 2.63 (m, 2H), 2.15
 - as a white solid
- <u>C.n.4-{3-(S)-[(Methanesulfonýl)-(3-phenylpropyl)amino]-2-oxopyrrolidin-1-ylmethyl}thlöphene-2-carboxamidine-trifluoroacetate.</u>

 Methanesulfonic acid-[1-(5-cyanothiòphen-3-ylmethyl)-2-oxopyrrolidin-3-(S)
 - yl]-(3-phenylpropyl)amide is converted to the title compound as described in EXAMPLE 125, Part D. The crude product is purified by RP-HPLC eluting in a gradient of 10% CH₃CN/H₂O (0.1% TFA) to 80% CH₃CN/H₂O (0.1% TFA) and the appropriate product fractions are lyophilized to provide the title compound as a white solid.
 - 35 (m,1H, NMR (DMSO-d₆) 300 MHz) δ.9.28 (bs, 2H); 9.07 (bs, 2H); 7.90 (m,1H), 7.85 (m,1H), 7.23 (m, 2H), 7.15 (m, 3H), 4.55 (t, 1H), 4.40 (AB, 2H), 3.20 (m, 3H), μπτιμ Ο του Ευσωνού Ευσων

3,12, (ş, 3H), 3.07, (m, 1H), 2.56 (m, 2H), 2.31 (m, 1H), 1.91 (m, 3H)πFAB MS, [M+H]*=435.

EXAMPLE 133

EXAMPLE 132

5 4-{3-(S)-[(Methanesulfonyl)(naphthalene-2-yl)amino]-2-oxopyrrolidin-1-5 ylmethyl)thiophene-2-carboxamidine trifluoroacetate.

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A. Methanesulfonic acid-[1-(5-cyanothiophen-3-ylmethyl)-2-oxopyrrolidin-3-(S)-yl](naphthalene-2-yl)amide.

The title compound is prepared as in EXAMPLE 126, Part A using at the methanesulfonic acid-[1-(5-cyanothiophen-3-ylmethyl)-2-oxopyrrolidin-3-(S)-yl]amide, prepared as in EXAMPLE 132, Part A, in place of 7-methoxy-naphthalene-2-sulfonic acid-[1-(5-cyanothiophen-3-ylmethyl)-2-oxopyrrolidin-3-(S)-yl]amide and 2-naphthyl bromide in place of Mel to give the title compound as a white foam.

¹H NMR (CDCl₃, 300 MHz) δ 7,79 (m, 4H), 7.50 (m, 5H), 4.70 (m, 1H), 4.53 (m, 2H), 4.40 (m, 1H), 4.32 (m, 1H), 3.26 (s, 3H), 3.04 (m, 2H), 2.00 (m, 2H).

B. 4-{3-(S)-[(Methanesulfonyl)(naphthalene-2-yl)amino]-2-oxopyrrolidin-120 ylmethyl)thiophene-2-carboxamidine-trifluoroacetate: perconstruction of Methanesulfonic acid-[1-(5-cyanothiophen-3-ylmethyl)-2-oxopyrrolidin-3-(S)-yl](naphthalene-2-yl)amide is converted to the title compound as described in EXAMPLE-125, Part D. The crude product is purified by RP-HPLC eluting in a gradient of 10% CH₂CN/H₂O (0.1% TFA) to 80% CH₃CN/H₂O (0.1% TFA) and the appropriate product fractions are lyophilized to provide the title compound as a white solid.

¹H NMR (DMSO-d₆, 300 MHz) δ, 9.25 (bs, 2H), 9.12 (bs, 2H), 7.86 (m, 5H), 7.49 (m, 4H), 4.70 (m, 2H), 4.36 (m, 3H), 3.23 (s, 3H), 3.02 (m, 2H), 2.10 (m, 1H),

1.71 (m, 1H). FAB MS, [M+H] = 457 on. vo 3)-1}-Los o'nolle ensileM

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4,5-dichlorothiophene-2-sulfonyl chloride in place of 7-methoxynaphthalene-2sulfonyl chloride to give the title compound as a white foam. ¹H NMR (CDCl₃, 300 MHz) δ 7.62 (m, 1H), 7.45 (m, 4H), 5.52 (s, 1H), 4.49 (s, 2H), 3.92 (m, 1H), 3.26 (m, 2H), 2.61 (m, 1H), 2.08 (m, 2H).

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B. 4.5-Dichlorothiophene-2-sulfonic acid-11-(5-cvanothiophen-3-vlmethyl)-2oxopyrrolidin-3-(S)-yi]benzylamide.

The title compound is prepared as in EXAMPLE 126, Part A using 4,5-dichlorothiophene-2-sulfonic acid [1-(5-cyanothiophen-3-ylmethyl)-2oxopyrrolidin-3-(S)-yl]amide in place of 7-methoxynaphthalene-2-sulfonic acid [1-(5-cyanothiophen-3-ylmethyl)-2-oxopyrrolidin-3-(S)-ŷl]amide and benzyl bromide in place of Mel to give the title compound as a white foam. 51 H NMR (CDCl₃, 300 MHz) δ 7.61 (s, 1H), 7.46 (m, 2H), 7.32 (m, 2H), 7.26 (m, 3H), 4.56 (m, 2H), 4.40 (t, 1H), 4.37 (AB, 2H), 3.04 (m, 2H), 2.15 (m, 1H), 1.90 (m: 2H), at the hord standances educate goal are of of the Out to asked

C. 4-(3-(S)-[(4.5-Dichlorothiophene-2-sulfonyl)benzylamino]-2-oxopyrrolidin-1-vlmethyl}thiophene-2-carboxamidine trifluoroacetate. 4,5-Dichlorothiophene-2-sulfonic acid [1-(5-cyanothiophen-3-ylmethyl)-2-

For three to provide the compound as a will a son-

- oxopyrrolidin-3-(S)-yl]benzylamide is converted to the title compound as 20 described in EXAMPLE 125, Part D. The crude product is purified by RP-HPLC eluting in a gradient of 10% CH₂CN/H₂O (0.1% TFA) to 80% CH₂CN/H₂O (0.1% TFA) and the appropriate product fractions are lyophilized to provide the title compound as a white solid.
 - 25 1H NMR (DMSO-d₆, 300/MHz) δ 9.21 (bs, 2H), 9.00 (bs, 2H), 7.92 (m. 1H), 7.89 (m,4H),7.81 (m,1H),7.26 (m,5H),4.76 (m,1H),4.76 (t,1H),4.58 (m,1H),4.32 (AB, 2H), 4.19 (m, 1H), 3.11 (m, 1H), 3.00 (m, 1H), 2.10 (m, 1H), 1.62 (m, 1H). FAB: MS, [M+H] = 543. Elemental analysis cal. C=42.01%, H=3.22%, N=8.52%, found C=41.73%, H=3.23%, N=8.29%. 30 Sec. ((High 87.7 gH) by 68.7 dec. (6) 58.8 6 (xHM 300 gC 60.1) (AMM H) 30

- 1.5. (**EXAMPLE 135** (a) 30つ (位) かしても ((は (8A) 74 り (46 (m)) ここ ((け) 4-(3-(S)-[(5-Chloro-3-methylbenzo[b]thlophene-2-sulfonyl)methylamino]-2oxopyrrolidin-1-ylmethyl)thiophene-2-carboxamidine trifluoroacelate. 11. 3-Carnarian and Informed Asylinative Second Security Second S

35. Apr 5-Chloro-3-methylbenzo[b]thiophene-2-sulfonic acid [1-(5-cvanothlophen-3-ylmethyl)-2-oxopyrrolldin-3-(S)-vii-methylamide o ethoxycaphinalane 2-buttony/homing-t-phanothulace, unide la noisy, laborational

۲G.

The title compound is prepared as in EXAMPLE-126, Part A using 5-chloro-3-methylbenzo[b]thiophene-2-sulfonic acid [1-(5-cyanothlophen-3-ylmethyl)-2-oxopyrrolidin-3-(S)-yl]-benzylamide in placetof 7-methoxynaphthalene-2-sulfonic acid [1-(5-cyanothlophen-3-ylmethyl)-2-oxopyrrolidin-3-(S)-yl]amide to

5 afford the title compound as a white solid.

1H NMR (CDCI₃, 300 MHz) δ.7.79 (m, 2H), 7.42 (m, 3H), 4.87 (t, 1H); 4.40 (AB,

2H), 3.26 (m, 2H), 2.88 (s, 2H), 2.70 (s, 3H), 2.41 (m, 1H), 2.05 (m, 1H).

pnisu A 7-99 38 (3-19MAXB of an bargueric at bargamen attit and B. 4-(3-(S)-[(5-Chloro-3-methylbenzo[b]thiophene-2-sulfonyl)methylamino]-2-10 oxopyrrolidin-1-ylmethyl)thiophene-2-carboxamidine trifluoroacetate. 0: 17-5-Chloro-3-methylbenzo[b]thiophene-2-sulfonic acid-[1-(5-cyanothiophen-3-19-3-methylbenzo[b]thiophene-2-sulfonic acid-[1-(5-cyanothiophen-3-19-3-methylbenzo[b]thiophene-2-sulfonic acid-[1-(5-cyanothiophen-3-19-3-methylbenzo[b]thiophene-3-19-3-meth

ylmethyl)-2-oxopyrrolidin-3-(S)-yll-methylamide is converted to the title compound as described in EXAMPLE 125, Part D2The crude product is purified by RR-HPLC eluting in a gradient of 10% CH₃CN/H₂O (0.1%:TFA) to 80% CH₂CN/H₂O (0.1%:TFA)

15 80% CH₃CN/H₂O (0.1% TFA) and the appropriate product fractions are lyophilized to provide the title compound as a white solid.

¹H NMR (DMSO-d_e, 300 MHz) δ.9.21, (bs. 2H), 8.85 (bs. 2H), 8.10 (m, 2H), 7.91 (s. 1H), 7.81 (s. 1H), 7.60 (m, 1H), 4.88 (t. 1H), 4.37 (AB, 2H), 3.21 (m, 2H), 2.75 (s. 3H), 2.65 (s. 3H), 2.09 (m, 1H), 1.92 (m, 1H), FAB MS, [M+H]*=497.

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EXAMPLE 136

CH-CH CONDITION SCHOOL TO BE SOUTH OF SOUTH O

25 A. 2-[[1-(5-Cyanothiophene-3-ylmethyl)-2-oxopyrrolidin-3-(S)-yl]-(7-) 35 methoxynaphthalene-2-sulfonyl)amino]-N-phenethylacetamide:Ht.m)

The tittle compound is prepared as described in EXAMPLE 127, Part C, substituting phenethyl amine for NH,OH. The tittle compound is obtained as a white foam.

30 ¹H NMR (CDCl₃, 300 MHz) δ 8.38 (s, 1H), 7.89 (m, 1H), 7.78 (m, 1H), 7.55 (s, 1H), 7.21 (m, 6H), 4.47 (AB, 2H), 4.30 (m, 1H), 3.92 (s, 3H), 3.76 (AB, 2H), 3.31 (m, 2H), 2.61 (m, 2H), 2.28 (m, 1H), 3.90 (m, 2H), 2.61 (m, 2H), 2.28 (m, 1H), 3.90 (m, 2H), 2.61 (m, 2H), 2.28 (m, 2H), 3.90 (m,

B. 2-[[1-(5-Carbamimidoylthiophene-3-ylmethyl)-2-oxopyrrolidin-3-(S)-yl]-(7-methoxynaphthalene-2-sulfonyl)amino]-N-phenethylacetamide trifluoroacetate.

2-[[1-(5-Cyanothiophene-3-ylmethyl)-2-oxopyrrolidin-3-(S)-yl]-(7-wl-£ methoxynaphthalene-2-sulfonyl)amino]-N-phenethylacetamide is converted to

the title compound as described in EXAMPLE 125, Part D. The crude product is purified by RP-HPLC eluting in a gradient of 10% CH₃CN/H₂O (0.1% TFA) to 80% CH₃CN/H₂O (0.1% TFA) and the appropriate product fractions are lyophilized to provide the title compound as a white solid.

¹H NMR (DMSO-d₆, 300 MHz) δ 9.21 (bs, 2H), 8.99 (bs, 2H), 8.41 (s, 1H), 8.15 (m, 1H), 7.95 (m, 2H), 7.78 (m, 2H), 7.55 (m, 1H), 7.35 (m, 1H), 7.18 (m, 5H), 4.78 (t, 1H), 4.38 (AB, 2H), 3.89 (s, 3H), 3.86 (m, 1H), 3.62 (m, 3H), 3.18 (m, 2H), 2.51 (m, 2H), 2.02 (m, 2H). FAB MS, [M+H]*=620.

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10 A EXAMPLE 137 A STRUMENT A STORY STAR BOWL

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2-[[1-(5-Carbamimidoylthiophene-3-ylméthyl)-2-oxopyrrolidin-3-(\$)-ŷl]-(4.5-dichlorothiophene-2-sulfonyl)amino]-N-benzylacetamide trifluóroacètate.

A. 2-[[1-(5-Cyanothiophene-3-vimethyl)-2-oxopyrrolidin-3-(S)-vi]-(4.5-dichlorothiophene-2-sulfonyl)aminolacetic acid tert-butyl ester.

The title compound is prepared as in EXAMPLE 126, Part A using tert-butyl-bromoacetate in place of MeI to give the title compound as a white foam.

¹H NMR (CDCl₃, 300 MHz) δ 7.60 (s, 1H), 7.49 (s, 1H), 7.42 (s, 1H), 4.42 (m, 3H), 3.89 (AB, 2H), 3.72 (m, 1H), 3.27 (m, 2H), 2.55 (m, 1H), 2.34 (m, 1H), 1.44 (s, 9H).

B. 2-[[1-(5-Cyanothiophene-3-ylmethyl)-2-oxopyrrollidin-3-(S)-yl]-(4.5-dichlorothiophene-2-sulfonyl)amino]acetic acid.

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To a solution of 2-[[1-(5-cyanothlophene-3-ylmethyl)-2-oxopyrrolidin-3-(S)-yl]25 (4,5-dichlorothlophene-2-sulfonyl)amino]ācētic acid tert-butyl ester (0.40 g, 0.72 mmol) in 15 mL of CH₂Cl₂ is added 5 mL of TFA. After 2 hours, the solution is concentrated to give the title compound as a white foam.

1H NMR (CDCl₃, 300 MHz) δ 7.98 (s, 1H), 7.89 (s, 1H), 7.81 (s, 1H), 4.80 (t, 1H), 4.32 (AB, 2H), 3.88 (AB, 2H), 3.19 (m, 2H), 2.22 (m, 1H), 2.08 (m, 1H).

C. 2-[[1-(5-Cyanothiophene-3-yimethyl)-2-oxopyrrolidin-3-(S)-yi]-(4.5-dichlorothiophene-2-sulfonyl)amino]-N-benzylacetamide.

The title compound is prepared as described in EXAMPLE 127, Part C, substituting 2:[[1:(5-Cyanothiophene-3-yimethyi)-2-oxopyrrolidin-3-(5)-yi]-(4,5-ydichlorothiophene-2-sulfonyi)aminojacetic acid for 2-[[1-(5-cyanothiophene-3-ylmethyi)-2-oxopyrrolidin-3-(5)-yi]-(7-methoxynaphthalene-2-

compound as described in EXAMPLE 121 Part D. Trong your Education

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1 4 3	, as all only familial actions and substituting phenetry amine for NH2OH. The
(437	्title compound is obtained as a white foam :
	1H), 3.86 (AB, 2H), 3.39 (m, 1H), 3.22 (m) 1H), 2.42 (m), 1H), 2.22 (m) 1H).
	5 14 NMR (CMSO-d _a , 300 MHz) 5 9.21 (bs, 2H), 6.39 (bs:H), 5 41 (c, :i-
(F17)	D. 2-[[1-(5-Carbamimidoylthiophene-3-ylmethyl)-2-oxopyrrollidin-3-(S)-yll-(4.5-
ا رندن	dichlorothiophene-2-sulfonyl)amino]-N-benzylacetamide trifluoroacetate
	2-[[1-(5-Cyanothiophene-3-ylmethyl)-2-oxopyrrolidin-3-(S)-vl]-(7-18-8
	methoxynaphthalene-2-sulfonyl)amino]-N-phenethylacetamide is converted to
10	the title compound as described in EXAMPLE 125, Part D. The crude product
10.74	is purified by RP-HPLC eluting in a gradient of 10% CH ₂ CN/H ₂ O (0.1% TFA) to
.91	80% CH ₃ CN/H ₂ O (0.1% TFA) and the appropriate product fractions are
	lyophilized to provide the title compound as a white solid.
4-	¹ H NMR (DMSO-d _s , 300 MHz) δ 9.22 (bs, 2H), 9.11 (bs, 2H), 8.56 (m, 1H), 7.92
15	(S, 1H), 7.89 (S, 1H), 7.78 (S, 1H), 7.26 (m, 4H), 4.79 (t/1H), 4.39 (m, 2H), 3.89
4.395	: 大学と そした 名うないに そのに名とな (前点) H); 2:10 (m/s1H)): FAB/MS2[M#H][準600.
٠	Elemental analysis calculated C=41.50%; H=3:48%; N=9.68%, found
3 (13)	C=41.48% H=3.21% N=8.68, F (1) 1 14 € HM 008 JOOC 1974 H
	5(1) 3.89 (AP. 2H), 3.7(100, 101, 0.2) (in, 25)), 2.52 (in, 14) (in, 15)
20	EXAMPLE 138 (HC.E) US
	2-[[1-(5-CarbamimIdoyIthiophene-3-ylmethyl)-2-oxopyrrolidin-3-(S)-yl]-(7-
	methoxynaphthalene-2-sulfonyl)amino]-N-benzylacetamide trifluoroacetate.
	clichtomhicahene-2 suifonyt) are in all suite and continuous A 2-111-6-Cyanothicahene 2 suite all suite and continuous and con
)\ 25	A. 2-[[1-(5-Cyanothiophene-3-ylmethyl)-2-oxopyrrölidin-3-(S)-yl]-(7-
- 3. 0	methoxynaphthalene-2-sulfonyl)amino]-N-benzylacetamidelololololololololololololololololololo
	The tiltle compound is prepared as described in EXAMPLE 127; Part C, substituting benzyl amine for NH ₄ OH ₁₀ The title compound is obtained as a
	white foam, so we was a second to the compound is obtained as a
.1 :.	white foam. (P.C.) (P.C
30	¹ H NMR (CDCl ₃ , 300 MHz) δ 8.35 (s, 1H), 7.76 (m, 2H), 7.49 (m, 1H), 7.23 (m, 9H), 4.40 (m, 5H), 3.94 (s, 3H), 3.86 (AB, 2H), 3.36 (m, 1H), 3.24 (m, 1H), 2.31
	(m, 2H).
	(m, 2H)(2) - 5-divilonivae ser 2-divisional - 0-analyseithness 0 - 6-11-0
	<u>B. 2-[[1-(5-Carbamimidoylthlophene-3-ylmethyl)-2-oxopyrrolidin-3-(S)-yl]-(7-</u>
	methoxynaphthalene-2-sulfonyl)amino]-N-benzylacetamide trifluoroacetate.
5	2-[[1-(5-Cyanothiophene-3-ylmethyl)-2-oxopyrrolidin-3-(S)-yl]-(7-methoxy-
a service	naphthalene-2-sulfonyl)amino]-N-benzylacetamide is converted to the title
	compound as described in EXAMPLE 125. Part D. The crude product is

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purified by RP-HPLC eluting in a gradient of 10% CH_3CN/H_2O (0.1% TFA) to 80% CH_3CN/H_2O (0.1% TFA) and the appropriate product fractions are lyophilized to provide the title compound as a white solid.

¹H NMR (CD_3OD , 300 MHz) δ 8.80 (m, 1H), 8.42 (s, 1H), 7.87 (m, 5H), 7.36 (m, 2H), 7.20 (m, 5H), 4.82 (m, 1H), 4.50 (AB, 2H), 4.32 (m, 2H), 3.92 (m, 5H), 3.30 (m, 2H), 2.30 (m, 1H), 2.05 (m, 1H). FAB MS, [M+H] $^+$ =606.

EXAMPLE 139

2-[[1-(4-Carbamimidoylthiophene-2-ylmethyl)-2-oxopyrrolidin-3-(S)-yl]-(7-methoxynaphthalene-2-sulfonyl)aminolacetamide trifluoroacetate.

ro a nar roller to the got r

A. 2-[[1-(4-Cyanothiophene-2-ylmethyl)-2-oxopyrrolidin-3-(S)-yl]-(7-methoxynaphthalene-2-sulfonyl)amino]acetic acid tert-butyl ester. The title compound is prepared as in EXAMPLE 126, Part A substituting 7-methoxynaphthalene-2-sulfonic acid [1-(4-cyanothiophen-2-ylmethyl)-2-oxopyrrolidin-3-(S)-yl]amide for 7-methoxynaphthalene-2-sulfonic acid [1-(5-cyanothiophen-3-ylmethyl)-2-oxopyrrolidin-3-(S)-yl]amide and tert-butyl-bromoacetate in place of Mel to give the title compound as a white foam. ¹H NMR (CDCl₃, 300 MHz) δ 8.42 (s, 1H), 7.82 (m, 4H), 7.27 (m, 2H), 7.15 (s, 1H), 4.66 (m, 1H), 4.15 (m, 1H), 3.92 (s, 3H), 3.68 (m, 1H); 3.28 (m, 2H), 2.56 (m, 1H), 2.40 (m, 1H), 1.41 (s, 9H).

- B. 2-[[1-(4-Cyanothiophene-2-ylmethyl)-2-oxopyrrolidin-3-(S)-yl]-(7-6-methoxynaphthalene-2-sulfonyl)aminolacetic acidasisma damacama.
- 30 C. 2-[[1-(4-Cyanothiophene-2-ylmethyl)-2-oxopyrrolidin-3-(\$)-yl]-(7-6)

 methoxynaphthalene-2-sulfonyl)amino]acetamide.006, 2003, 5044.

 The tiltle compound is prepared as described in EXAMPLE 127, Part C, substituting 2-[[1-(4-cyanothiophene-2-ylmethyl)-2-oxopyrrolidin-3-(\$)-yl]-(7-methoxynaphthalene-2-sulfonyl)amino]acetic acid for 2-[[1-(5-cyanothiophene-
- 35 3-ylmethyl)-2-oxopyrrolidin-3-(S)-yl]-(7-methoxynaphthaleñe-2-sulfonyl)amino]acetic acid. The title compound is obtained as a white foam.

. 9

(m, 1H), 14.64 (m, 3H); 3.94 (s, 3H), 3.72 (AB, 2H); 3.36 (AB, 2H); 2.35 (m, 1H), 2.16 (m, 1H). Short flow a natheracement of the order of the control of th

- D: 2-[[1-(4-Carbamimidov|thiophene-2-v|methyl)-2-oxopyrrolidin-3-(S)-yl]-(7-methoxynaphthalene-2-sulfonyl)aminojacetamide trifluoroacetate.

 2-[[1-(4-Cyanothiophene-2-ylmethyl)-2-oxopyrrolidin-3-(S)-yl]-(7-methoxynaphthalene-2-sulfonyl)aminoj-N-benzylacetamide is converted to the title compound as described in EXAMPLE 125, Part D. The crude product is
 - purified by RP-HPLC eluting in a gradient of 10% CH₃CN/H₂O to 80% CH₃CN/H₂O and the appropriate product fractions are lyophilized to provide the title compound as a white solid density and 100 d'onzy 11 (bs, 4H), 8.48 (m, 2H), 7.98 (m, 2H), 7.74 (m, 1H), 7.54 (m, 3H), 7.35 (m, 1H), 7.21 (m, 1H), 4.79 (t, 1H), 4.53 (ÅB, 2H),
 - 15 (3:89.(s,:3H); 3.64 (AB, 2H), 3.21 (m, 2H), 2.04 (m, 2H). FAB MS, [M+H] *=516. Elemental analysis calculated with 1.75 mmol of H₂O cal. C=47.34%, H=5.10%, N=12.00%, Cl=6.08%, found C=47.30%, H=4.82%, N=11.75, Cl=6.02%.

21 EXAMPLE(140)(1:45-4) 18 7 (2:42-2) 8 8 8 (2:44-0)(0:44-2)

- 20 2-[[1-(4-Carbamimidoŷlthiopheñe-2-ylmethyl)-2-oxopyrrolidin-3-(S)-yl]-(5-chloro-3-methylbenzo[b]thiophene-2-sulfonyl)aminolacetic acid methyl ester.
 - A. 2-[[1-(5-Cyanothiophene-3-ylmethyl)-2-oxopyrrolidin-3-(5)-yl]-(7-methoxynaphthalene-2-sulfonyl)aminolacetic acid methyl ester.
- The title compound is prepared as in EXAMPLE 126, Part A substituting 5-chloro-3-methyl-benzo[b]thiophene-2-sulfonic acid-[1-(5-cyanothiophen-3-ylmethyl)-2-oxopyrrolidin-3-(S)-yl]amide for 7-methoxynaphthalene-2-sulfonic acid-[1-(5-cyanothiophen-3-ylmethyl)-2-oxopyrrolidin-3-(S)-yl]amide and substituting methyl-bromoacetate for Mel to give the title compound as a white foam.
 - ¹H NMR (CDCl₃, 300 MHz) δ.7.80 (s; 1H), 7.76 (d, 1H), 7.45 (m; 2H), 7.39 (s, 1H), 4.64 (t, 1H); 4.40 (m; 2H), 4.18 (m, 2H); 3.52 (s, 3H); 3.33 (m, 2H), 2.69 (s, 3H), 2.55 (m; 1H), 2.38 (m; 1H). (3-snadqointensys b) [1]-S animisous
- 35 B. 2-[[1-(5-Cyanothiophene-3-ylmethyl)-2-oxopyrrolldin-3-(S)-yl]-(5-chloro-3-methyl-benzo[b]thiophene-2-sulfonyl)amino]acetic acid methyl ester.

- 10

2-[[1-(5-Cyanothiophene-3-ylmethyl)-2-oxopyrrolidin-3-(S)-yl]-(7-methoxynaphthalene-2-sulfonyl)amino]acetic acid methyl ester is converted to the title compound as described in EXAMPLE 125, Part D. The crude product is purified by RP-HPLC eluting in a gradient of 10% CH₃CN/H₂O (0.1% TFA) to 80% CH₃CN/H₂O (0.1% TFA) and the appropriate product fractions are lyophilized to provide the title compound as a white solid.

¹H NMR (DMSO-d₆, 300 MHz) δ 9.26 (bs, 2H), 9.18 (bs, 2H), 8.06 (m, 2H), 7.90 (s, 2H), 7.81 (s, 1H), 7.60 (m, 1H), 4.75 (t, 1H), 4.30 (AB, 2H), 4.01 (AB, 2H), 3.58 (s, 3H), 3.20 (m, 2H), 2.62 (s, 3H), 2.28 (m, 1H), 2.07 (m, 1H). FAB MS, [M+H]*=555.

EXAMPLE 141

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are commented that the same of the

A. N-Cbz-7-aminonaphthalene-2-sulfonic acid, sodium salt.

To a suspension of 7-aminonaphthalene-2-sulfonic acid, sodium salt (10.1 g, 41.2 mmol) in 200 mL of water is added solid NaOH (3.29 g, 82.4 mmol) at room temperature. The mixture is stirred for 1 hour, and then benzyl

chloroformate (11.8 mL, 82.4 mmol) is added. A precipitate forms after 30 min and the resulting mixture is stirred over a period of 18 hours. The crude mixture is concentrated in vacuo and the residue is stirred in 100 mL of absolute EtOH as a slurry for 2 hours. The precipitate is filtered and dried. The

solid is heated at reflux in 100 mL of 95% EtOH for 2 hours, allowed to cool to

25... roomitemperature filtered and dried to give 15.4 g of the title compound. H NMR (DMSO-d_s, 300 MHz) δ 8.06 (s, 1H), 7.97 (s, 1H), 7.82 (d, 1H), 7.77 (d, 8.1H), 7.61 (dd, 1H), 7.58 (dd, 1H), 7.41 (m, 5H), 5.18 (s, 2H).

15 J. 7.14 (c. 14g, 7.50 (d. 14f) 7.67 (m. 34f), 7.26 (n. 5H), 6.79 (AE), 23f

B. N-Cbz-7-aminonaphthalene-2-sulfonyl chloride. BA) Co. (11)

N-Cbz-7-aminonaphthalene-2-sulfonic acid, sodium salt (15.4 g, 40.7 mmol) is converted to the title compound as described in EXAMPLE 125; Part B. The crude product is purified by column chromatography in a gradient of hexanes were 20% EtOAc/hexanes to afford the title compound (5 g, 13.3 mmol) as a beige crook eligible of the bar over a significant of the compound (5 g, 13.3 mmol).

35 36 H-NMR (CDCl₃, 300 MHz) δ 8.38 (s, 1H), 8.12 (s, 1H), 7.88 (d, 1H), 7.80 (d, 2H), 7.60 (dd, 1H), 7.34 (m, 5H), 7.27 (s, 1H), 5.21 (s, 2H), 7.60 (dd, 1H), 7.34 (m, 5H), 7.27 (s, 1H), 5.21 (s, 2H), 7.60 (dd, 1H), 7.34 (m, 5H), 7.27 (s, 1H), 5.21 (s, 2H), 7.60 (dd, 1H), 7.34 (m, 5H), 7.27 (s, 1H), 5.21 (s, 2H), 7.60 (dd, 1H), 7.34 (m, 5H), 7.27 (s, 1H), 7.21 (s, 2H), 7.60 (dd, 1H), 7.34 (m, 5H), 7.27 (s, 2H), 7.60 (dd, 1H), 7.34 (m, 5H), 7.27 (s, 2H), 7.60 (dd, 1H), 7.34 (m, 5H), 7.27 (s, 2H), 7.60 (dd, 1H), 7.34 (m, 5H), 7.27 (s, 2H), 7.60 (dd, 1H), 7.34 (m, 5H), 7.27 (s, 2H), 7.60 (dd, 1H), 7.34 (m, 5H), 7.27 (s, 2H), 7.60 (dd, 1H), 7.34 (m, 5H), 7.27 (s, 2H), 7.60 (dd, 1H), 7.34 (m, 5H), 7.27 (s, 2H), 7.60 (dd, 1H), 7.34 (m, 5H), 7.27 (s, 2H), 7.60 (dd, 1H), 7.34 (m, 5H), 7.27 (s, 2H), 7.60 (dd, 1H), 7.34 (m, 5H), 7.27 (s, 2H), 7.60 (dd, 1H), 7.34 (m, 5H), 7.27 (s, 2H), 7.27 (s

C. -N-Cbz-7-aminonaphthalene-2-sulfonic acid-[1-(5-cyanothiophen-3-cyanothiophen-3-cyanothiophen-3-cyanothiophen-3-cyanothiophen-3-cyanothiophene-2-cyanothioph

EKANFLE 141

<u>Vimethyl)-2-oxopyrrolidin-3-(S)-yl]benzylamide.S-ageripoid (Criesply</u>

(m, 1H), 3.14 (m, 2H), 2.47 (m, 1H), 1.99 (m, 1H).

- N-Cbz-7-aminonaphthalene-2-sulfonic acid-[1-(5-cyanothiophen-3-ylmethyl)-2-oxopyrrolidin-3-(S)-yl]amide (0.56 g, 1.01 mmol) is dissolved in 10 mL of DMF and cooled to 0°C. Sodium hydride (42 mg of a 60% dispersion in mineral oil, 1.06 mmol) is added and the solution is stirred for 20 minutes. To the mixture is added benzyl bromide (0.18 g, 1:06 mmol). The reaction mixture
- 20. is stirred at 0°C for 20minutes and then at room temperature for 1.5 hours. The solution is poured into a separatory funnel and diluted with 100 mL of EtOAc.

 The organic layer is washed with water of NHCI and saturated NaCI solution, then dried over MgSOm filtered and concentrated a The crude residue is
- 25 priffied by column chromatography eluting with a gradient of 25% 25 pr. EtOAc/CH₂Cl₂ to 50% EtOAc/CH₂Cl₂ to give the title compound (0.34:g, 0.53 mmol) as a solid. 70.7 (Hr. ε) 80.8 δ (xHw 005 , b-O2MC) HMV H H NMR (CDCl₃, 300 MHz), δ 8:39 (s, 1H), 8.08 (s, 1H), 7.86 (d, 1H), 7:78 (d, 1H), 7.74 (s, 1H), 7.60 (d, 1H), 7.37 (m, 8H), 7.25 (m, 5H), 5.19 (AB, 2H), 4.52 (m, 1H), 4.39 (AB, 2H), 4:34 (AB, 2H), 2.92 (m, 2H), 2.16 (m, 1H), 1.87 (m, 1H).

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E. 4-{3-(S)-[(7-Aminonaphthalene-2-sulfonyl)benzylamino]-2-oxopyrrolidin-1-ylmethyl)thiophene-2-carboxamidine bistrifluoroacetate cubort, ebuto

N-Cbz-7-aminonaphthalene-2-sulfonic acid-[1-(5-cyanothiophen-3-ylmethyl)-2-oxopyrrolidin-3-(S)-yl]-benzylamide is converted to the title compound as

35 described in EXAMPLE 125, Part D. The crude product is purified by RP-HPLC eluting in a gradient of 10% CH₃CN/H₂O (0.1% TFA) to 60% CH₃CN/H₂O (0.1%

TFA) and the appropriate product fractions are lyophilized to provide the title compound as a white solid.

¹H NMR (DMSO-d_s, 300 MHz) δ 9.26 (bs, 2H), 9.04 (bs, 2H), 8.14 (s, 1H), 7.81 (m, 3H), 7.73 (d, 1H), 7.55 (dd, 1H), 7.32 (m, 2H), 7.25 (m, 3H), 7.11 (dd, 1H),

- 7.01 (s, 1H), 4.73 (m, 1H), 4.35 (AB, 2H), 4.29 (AB, 2H), 3.13 (m, 1H), 2.94 (m, 1H), 2.08 (m, 1H), 1.63 (m, 1H). FAB MS, [M+H]*=534. Elemental analysis calculated with 0.4 mol of H₂O: C=48.42%, H=3.91%, N=9.11%; found C=48.42%, H=4.06%, N=9.11%.

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- A. N-Cbz-7-aminonaphthalene-2-sulfonic acid [1-(5-cyanothiophen-3-15 ylmethyl)-2-oxopyrrolidin-3-(S)-yllmethylamide.
- The title compound is prepared from N-Cbz-7-aminonaphthalene-2-sulfonic acid [1-(5-cyanothiophen-3-ylmethyl)-2-oxopyrrolidin-3-(S)-yl]amide as described in EXAMPLE 141, Part D using methyl iodide in place of benzyl bromide. The crude product is purified by column chromatography eluting with
- 20 10% EtOAc/CH₂Cl₂ to afford the title compound as a solid.

 1H.NMR (CDCl₃, 300 MHz) δ 8.38 (s, 1H), 8.08 (s, 1H), 7.85 (d, 1H), 7.80 (dd, 1H), 7.77 (d, 1H), 7.40 (m; 8H); 7.21 (s, 1H), 5.24 (AB, 2H), 4.87 (m, 1H), 4.35 (AB, 2H), 3.22 (m, 2H), 2.79 (s, 3H), 2.35 (m, 1H), 2.05 (m, 1H).
- B. 4-(3-(S)-[(7-Aminonaphthalene-2-sulfonyl)methylamino]-2-oxopyrrolidin-1-ylmethyl)thlophene-2-carboxamidine bistrifluoroacetate.

 N-Cbz-7-aminonaphthalene-2-sulfonic acid [1-(5-cyanothiophen-3-ylmethyl)-2-oxopyrrolidin-3-(S)-yl]methylamide is converted to the title compound as described in EXAMPLE 125, Part D. The crude product is purified by RP-HPLC eluting in a gradient of 10% CH₃CN/H₂O (0.1% TFA) to 60% CH₃CN/H₂O (0.1% TFA) and the appropriate product fractions are lyophilized to provide the title compound as a white solid.
- (s; 1H), 7.82 (d, 1H), 7.80 (s, 1H), 7.73 (d, 1H), 7.43 (d, 1H), 7.12 (dd, 1H), 7.01
- 35: (s; 1H), 4.86 (m; 1H), 4.37 (AB, 2H), 3.15 (m, 2H), 2.64 (s, 3H), 1.95 (m, 1H), 1.74 (m, 1H). FAB MS, [M+H] = 458. Elemental analysis calculated: C=43.80%, H=3.68%, N=10.21%; found C=43.40%, H=3.75%, N=10.00%.

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TFA) and the abpropriate productinactions are "voobliked to provide the title **EXAMPLE 143** compound as a white solia. 2-[[1-(5-Carbamimidovlthiophene-3-ylmethyl)-2-oxopyrrolidin-3-(S)-vII-(7aminonaphthalene-2-sulfonyl)amino]acetamide bistrifluoroacetate.) 7.01 (s, 1H), 4.75 (m, 1H), 4.35 (AB, 9H), 4.29 (AB, 2H), 3.13 (m, 1H). 2-[[1-(5-Cyanothiophene-3-ylmethyl)-2-oxopyrrolidin-3-(S)-yll-(N-Cbz-7aminonaphthalene-2-sulfonyl)aminolacetic acid tert-butyl esteruolso The title compound is prepared from N-Cbz-7-aminonaphthalene-2-sulfonic acid [1-(5-cyanothiophen-3-ylmethyl)-2-oxopyrrolidin-3-(S)-yl]amide as described in EXAMPLE 141, Part D using tert-butyl bromoacetate in place of benzyl bromide. The crude product is purified by column chromatography eluting with a gradient of 5% EtOAc/CH2CL to 10% EtOAc/CH2Cl2 to provide the title compound as a solid. ¹H NMR (CDCI₃, 300 MHz) δ.8.45 (s. 1H), 8.10 (s. 1H), 7.87 (m) 2H), 7.80 (d, 15 1H), 7.55 (dd, 1H), 7.45 (m, 7H), 7.01 (m, 1H), 5.30 (s, 2H), 4.55 (m, 1H), 4.40 (AB, 2H), 3.92 (AB, 2H), 3.32 (m, 1H), 3.21 (m, 1H), 2.60 (m, 1H); 2.45 (m, 1H), and (i-(5-cyanothic reen-3-virethyl)-2-oxopyemildin-3-(5)-Yijamide as cosoribed in EXAMPLE 141 Pact Clusting methyl lookle in place of ponzyt 2-[[1-(5-Cyanothiophene-3-ylmethyl)-2-oxopyrrolidin-3-(S)-yll-(N-Cbz-7offw policy **20** aminonaphthalene-2-sulfonyl)aminolacetic acides 20, HONACIE & 01 2-[[,1-(5-Cyanothiophene-3-ylmethyl)-2-oxopyrrolidin-3-(S)-yll-(N-Cbz-7aminonaphthalene-2-sulfonyl)aminolacetic acid tert-butyl ester is converted to the title compound as described in EXAMPLE 127 Part B: The product is azeotroped with toluene/CH2Cl2 to give a white foam which is used directly in 25 the next step. B. 4-{3-(S)-(7:-Autrographthalene-2-sulfonyllmich FAB MS, [M+H] =619. Constitution of the consti N-Cbz 7-aminonaph*hidene-2-sulfon-c auld [1-f]-gvanot C. 2-I[1-(5-Cyanothiophene-3-ylmethyl)-2-oxopyrrolidin-3-(S)-yl]-(N-Cbz-7aminonaphthalene-2-sulfonyl)aminolacetamide: quaxit ni usdinoseis 30 The title compound is prepared as described in EXAMPLE 127, Part C using 2-[[1-(5-cyanothiophene-3-ylmethyl)-2-oxopyrrolidin-3-(S)-yl]-(N-Cbz-7aminonaphthalene-2-sulfonyl)amino]acetic acid in place of 2-[[1-(5-1900 cyanothiophene-3-ylmethyl)-2-oxopyrrolidin-3-(\$)-yl]-(7-methoxynaphthalene-2-sulfonyl)amino]acetic acid. The crude product is purified by column:

1.74 (m, 11-). FAB (AS. (New y) =458 (decret) 4.95 (m. 11-). FAB (AS. (New y) =458 (decret) 4.65 (m. 11-). (FAB (AS. (New y) 4.68 (decret) 4.

chromatography eluting with 2% MeOH/50% EtOAc/CH2Cl2 to provide the title

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¹H NMR (CDCl₃, 300 MHz) δ 8.40 (s, 1H), 8.09 (s, 1H), 7.82 (m, 2H), 7.75 (m, 2H), 7.60 (dd, 1H), 7.50 (m, 2H), 7.38 (m, 6H), 5.63 (bs, 1H), 5.25 (s, 2H), 4.51 (s, 1H), 4.43 (AB, 2H), 3.77 (AB, 2H), 3.38 (m, 1H), 3.25 (m, 1H), 2.39 (m, 1H), 2.21 (m, 1H).

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D. 2-[[1-(5-Carbamimidoylthiophene-3-ylmethyl)-2-oxopyrrolidin-3-(S)-yl]-(7-aminonaphthalene-2-sulfonyl)amino]acetamide bistrifluoroacetate.
2-[[1-(5-Cyanothiophene-3-ylmethyl)-2-oxopyrrolidin-3-(S)-yl]-(N-Cbz-7-aminonaphthalene-2-sulfonyl)amino]acetamide is converted to the title compound as described in EXAMPLE 125, Part D. The crude product is purified by RP-HPLC eluting in a gradient of 10% CH₃CN/H₂O (0.1% TFA) to 80% CH₃CN/H₂O (0.1% TFA) and the appropriate product fractions are lyophilized to provide the title compound as a white solid.

1H NMR (DMSO-d₆, 300 MHz) δ 9.26 (bs, 2H), 9.00 (bs, 2H), 8.12 (s, 1H), 7.92 (s, 1H), 7.82 (d, 1H), 7.81 (s, 1H), 7.73 (d, 1H), 7.58 (s, 1H), 7.48 (dd, 1H), 7.24 (s, 1H), 7.13 (dd, 1H), 7.01 (s, 1H), 4.78 (m, 1H), 4.38 (AB, 2H), 3.64 (AB, 2H), 3.20 (m, 2H); 2.09 (m, 1H), 1.97 (m, 1H). FAB MS, [M+H]*=501.

THE EXAMPLE 144 CONTROL OF THE PROPERTY OF THE

20 <u>4-[3-(S)-(6-Amino-5-chloro-2-sulfonylamino)-2-oxopyrrolidin-1-ylmethyl]-thiophene-2-carboxamidine trifluoroacetate.</u>

in our services (8) when independent interruption is

Ac N-Cbz-6-aminonaphthalene-2-sülfönic acid; södium salt. China s

B. N-Cbz-6-amino-5-chloro-naphthalene-2-sulfonyl chloride and N-Cbz-6-aminonaphthalene-2-sulfonyl chloride.

N-Cbz-6-aminonaphthalene-2-sulfonyl chloride.

N-Cbz-6-aminonaphthalene-2-sulfonic acid, sodium salit is converted to the title compounds as described in EXAMPLE 125, Part B. The crude mixture is purified by columnichromatography in a gradient of hexanes to 10% EtOAc/hexanes to provide N-Cbz-6-amino-5-chloro-naphthalene-2-sulfonyl chloride as the major component as a being solid.

(HINMR (CDC); 300 MHz) & 8.71 (d, 1H); 8.59 (s, 4H), 8.38 (d, 1H), 8.09 (dd, 1H); 7.96 (d, 1H); 7.65 (s; 1H); 7.41 (m; 5H), 5.30 (s; 2H); EliMS, [M]*=409.

(HINMR (CDC); 300 MHz) & 8.71 (d, 1H); 7.65 (s; 1H); 7.41 (m; 5H), 5.30 (s; 2H); EliMS, [M]*=409.

(HINMR (CDC); 300 MHz) & 8.71 (d, 1H); 8.59 (s; 4H); 8.38 (d; 1H); 8.09 (dd, 1H); 8.59 (s; 4H); 8.38 (d; 1H); 8.09 (dd, 1H); 8.59 (s; 4H); 8.38 (d; 1H); 8.09 (dd, 1H); 8.59 (s; 4H); 8.59 (s; 4H); 8.38 (d; 1H); 8.09 (dd, 1H); 8.59 (s; 4H); 8.38 (d; 1H); 8.09 (dd, 1H); 8.59 (s; 4H); 8.59 (s; 4H); 8.38 (d; 1H); 8.09 (dd, 1H); 8.59 (s; 4H); 8.38 (d; 1H); 8.09 (dd, 1H); 8.59 (s; 4H); 8.59 (s; 4H); 8.38 (d; 1H); 8.09 (dd, 1H); 8.59 (s; 4H); 8.59 (s; 4H); 8.59 (s; 4H); 8.59 (s; 4H); 8.09 (dd, 1H); 8.09 (dd, 1H); 8.59 (s; 4H); 8.59 (s; 4H); 8.09 (dd, 1H); 8.09 (dd, 1H); 8.59 (s; 4H); 8.59 (s; 4H); 8.09 (dd, 1H); 8.09 (dd,

5 ¹H NMR (CDCl₃, 300 MHz) δ 8.52 (s, 1H), 8.23 (m, 1H), 7.96 (m, 3H), 7.55 (dd, 1H), 7.43 (m, 5H), 7.01 (s, 1H), 5.30 (s, 2H) ± FAB MS, [M+H] ± 376.

<u>Guideosoroutinicid etimeteostonime(lynotius-S-oneteoridentidentide)</u>

V.S. C. N-Cbz-6-amino-5-chloro-naphthalene-2-sulfonic acid-[1-(5-cyanothiophen-entides)]

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- 10 The title compound is prepared from 4-(3-(S)-amino-2-oxopyrrolidin-1- (*)
 ylmethyl)thiophene-2-carbonitrile hydrochloride as described in EXAMPLE
 125. Rart C using N-Cbz-6-amino-5-chloro-naphthalene-2-sulfonyl chloride in place of 7-methoxynaphthalene-2-sulfonyl chloride. The crude product is
 concentrated from EtOAcito afford the title compound as a white solid.
- 15 [H NMR (CDC], 300 MHz) & 8.61 (d, 1H), 8.44 (s, 1H); 8.29 (d, 1H), 7.96 (dd, 1H), 7.90 (d, 1H); 7.60 (s, 1H); 7.43 (m, 6H), 7.39 (d, 1H), 5.55 (s, 1H), 5.29 (s, 2H), 4.42 (AB, 2H); 3.78 (m, 1H), 3.25 (m, 2H), 2.60 (m, 1H); 2.09 (m, 1H).
- D. 4-[3-(S)-(6-Amino-5-chloro-2-sulfonylamino)-2-oxòpyrrolidin-1-ylmethyl]20 thiophene-2-carboxamidine-trifluoroacetate. 110 3-ocumA-0 1-(3) 51-3 (3)
 N-Cbz-6-amino-5-chloro-naphthalene-2-sulfonic acid: [1-(5-cyanothiophen-3-ylmethyl)-2-oxopyrrolidin-3-(S)-yl]amide is converted to the title compound as described in EXAMPLE 125; Part D. The crude product is purified by RP-HPLC eluting in a gradient-of 10%, CH₃CN/H₂O to 60%, CH₃CN/H₂O and the
 - 25 appropriate product fractions are lyophilized to provide the title compound as a white solid acromound about the multiple of a circultus % englamines and 1H NMR (DMSO-d₆, 300 MHz) δ 9.25 (bs, 2H), 9.13 (bs, 2H), 8.25 (dd; 1H), 8.07 (d, 1H), 7.95 (d, 1H), 8.86 (s, 1H), 7.83 (dd; 1H), 7.80 (m; 2H), 7.22 (d, 1H) 4.34 (AB, 2H), 4.05 (m, 1H), 3.09 (m, 2H), 1.97 (m; 1H), 1.55 (m, 1H). FABINIS.
 - 30 [M+H]*=478. Elemental analysis calculated with 1.3 mol of H₂O: C=42.20%, H=3.78%, N=11.18%; found C=42.20%, H=3.36%, N=10.70%; 14.13

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A. N-Cbz-6-amino-5-chloro-naphthalene-2-sulfonic acid [1-(5-cyanothiophen-3-vlmethyl)-2-oxopyrrolidin-3-(S)-yl]-methylamide.

The title compound is prepared from N-Cbz-6-amino-5-chloro-naphthalene-2sulfonic acid [1-(5-cyanothiophen-3-ylmethyl)-2-oxopyrrolidin-3-(S)-yl]amide as described in EXAMPLE 141, Part D using methyl iodide in place of benzyl bromide. The crude product is purified by column chromatography eluting in a gradient of 10% EtOAc/CH2Cl2 to 25% EtOAc/CH2Cl2 to afford the title compound as a solid.sing the action of the figure of the solid state o

¹H NMR (CDCl₃, 300 MHz) δ 8.60 (d, 1H), 8.49 (d, 1H), 8.25 (d, 1H), 8.05 (dd, 10 1H), 7.95 (d, 1H), 7.60 (s, 1H), 7.44 (m, 7H), 5.30 (s, 2H), 4.93 (m, 1H), 4.40 (AB, 2H), 3,30 (m, 2H), 2.80 (s, 3H), 2.40 (m, 1H), 2.08 (m, 1H).

and appropriate the swittening to previously

B. 4-(3-(S)-[(6-Amino-5-chloro-naphthalene-2-sulfonvl)methylamino]-2oxopyrrolidin-1-vlmethyl}thiophené-2-carboxamidine trifluoroacetate.

N-Cbz-6-amino-5-chloro-naphthalene-2-sulfonic acid [1-(5-cyanothiophen-3-15 ylmethyl)-2-oxopyrrolidin-3-(S)-yl]-methylamide is converted to the title compound as described in EXAMPLE 125, Part D. The crude product is purified by RP-HPLC eluting in a gradient of 10% CH₃CN/H₂O to 80% CH₂CN/H₂O and the appropriate product fractions are lyophilized to provide the 20 title compound as a white solid; some off

¹H NMR (DMSO-d₆, 300 MHz) δ 9.26 (bs, 2H), 9.06 (bs, 2H), 8.29 (s, 1H), 7.94 (d, 1H), 7.90 (s, 1H), 7.84 (d, 1H), 7.81 (d, 1H), 7.79 (s, 1H), 7.23 (d, 1H), 4.85 (ma1H), 4.36 (AB, 2H), 3.13 (m, 2H), 2.63 (s, 3H), 1.97 (m, 1H), 1.73 (m, 1H). FAB MS, [M+H];=492. Elemental analysis calculated with 1.3 mol of H₂O:

25 C=43.89%, H=4.10%; N=11.13%; found C=43.90%, H=3.71%, N=10.62%. (क. 15% हे डेट) क्रा. 11th 285 fee. 1HC

EXAMPLE 146

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2-[[1-(5-Carbamimidoylthiophene-3-ylmethvl)-2-oxopyrrolldin-3-(S)-vl]-(6amino-5-chloronaphthalene-2-sulfonvl)aminolacetamide trifluoroacetate.

30: -3-5tC+17-[1, (3)-3-inbilition/gazza 2-i)/interpreter 2-(5) 11-2bz-6-3-(6) A: 2-[[1-(5-Cyanothiophene-3-ylmethyl)-2-oxopyrrollidin=3-(S)-vij-(N-Cbz-6amino-5-chloronaphthálene-2-súlfonvíl) aminolacetic acid tert-butyl ester. The title compound is prepared from N-Cbz-6-amino-5-chloro-naphthalene-2sulfonic acid-[1-(5-cyanothiophen-3-ÿlmethýl)-2-oxopyrrolidin-3-(S)-yl]amide as described in EXAMPLE 141, Part D using tent butyl bromoacetate in place of benzyl bromide: The crude product is purified by column chromatography THE COLOR THE TUBE TO THE TROOPS OF THE COLOR OF THE COLO

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eluting with a gradient of 5% EtOAc/CH₂Cl₂ to 10% EtOAc/CH₂Cl₂ to provide the title compound as a solid. A same to (6) 5-mt any goxo-School and the title compound as a solid. A same to (6) 5-mt any goxo-School and (6) 8.30-7.75 (m. 3H), 7.60-7.30 (m. 5H), 7.28-7.12 (m. 2H), 5.31-5.08 (m. 2H), 4.89-3.62 (m. 5H), 3.30 (m. 5H), 3.22 (m. 1H), 2.60 (m. 1H), 2.42 (m. 1H), 1.47 (s. 9H).

B. 2-[[1-(5-Cyanothiophene-3-ylmethyl)-2-oxopyrrolidin-3-(\$)-yl]-(N-Cbz-6-amino-5-chloronaphthalene-2-sulfonyl)aminolacetic acid: bhuochto 2-[[1-(5-Cyanothiophene-3-ylmethyl)-2-oxopyrrolidin-3-(\$)-yl]-(N-Cbz-6-amino-5-chloronaphthalene-3-ylmethyl)-2-oxopyrrolidin-3-(\$)-yl]-(N-Cbz-6-amino-5-chloronaphthalene-3-ylmethyl)-2-oxopyrrolidin-3-(\$)-yl]-(N-Cbz-6-amino-5-chloronaphthalene-3-ylmethyl)-2-oxopyrrolidin-3-(\$)-yl]-(N-Cbz-6-amino-5-chloronaphthalene-3-ylmethyl)-2-oxopyrrolidin-3-(\$)-yl]-(N-Cbz-6-amino-5-chloronaphthalene-3-ylmethyl)-2-oxopyrrolidin-3-(\$)-yl]-(N-Cbz-6-amino-5-chloronaphthalene-3-ylmethyl)-2-oxopyrrolidin-3-(\$)-yl]-(N-Cbz-6-amino-5-chloronaphthalene-3-ylmethyl)-2-oxopyrrolidin-3-(\$)-yl]-(N-Cbz-6-amino-5-chloronaphthalene-3-ylmethyl)-2-oxopyrrolidin-3-(\$)-yl]-(N-Cbz-6-amino-5-chloronaphthalene-3-ylmethyl)-2-oxopyrrolidin-3-(\$)-yl]-(N-Cbz-6-amino-5-chloronaphthalene-3-ylmethyl)-2-oxopyrrolidin-3-(\$)-yl]-(N-Cbz-6-amino-5-chloronaphthalene-3-ylmethyl)-2-oxopyrrolidin-3-(\$)-yl]-(N-Cbz-6-amino-5-chloronaphthalene-3-ylmethyl)-2-oxopyrrolidin-3-(\$)-yl]-(N-Cbz-6-amino-5-chloronaphthalene-3-ylmethyl)-2-oxopyrrolidin-3-(\$)-yl]-(N-Cbz-6-amino-5-chloronaphthalene-3-ylmethyl)-2-oxopyrrolidin-3-(\$)-yl]-(N-Cbz-6-amino-5-chloronaphthalene-3-ylmethyl)-2-oxopyrrolidin-3-(\$)-yl]-(N-Cbz-6-amino-5-chloronaphthalene-3-ylmethyl)-2-oxopyrrolidin-3-(\$)-yl]-(N-Cbz-6-amino-5-chloronaphthalene-3-ylmethyl)-2-oxopyrrolidin-3-(\$)-yl]-(N-Cbz-6-amino-5-chloronaphthalene-3-ylmethyl)-2-oxopyrrolidin-3-(\$)-yl]-(N-Cbz-6-amino-5-chloronaphthalene-3-ylmethyl)-2-oxopyrrolidin-3-(\$)-yl]-(N-Cbz-6-amino-5-chloronaphthalene-3-ylmethyl)-2-oxopyrrolidin-3-(\$)-yl]-(N-Cbz-6-amino-5-chloronaphthalene-3-ylmethyl)-2-oxopyrrolidin-3-(\$)-yl]-(N-Cbz-6-amino-5-chloronaphthalene-3-ylmethyl)-2-oxopyrrolidin-3-(\$)-yl]-(N-Cbz-6-amino-5-chloronaphthalene-3-ylmethyl)-2-oxopyrrolidin-3-(\$)-yl]-(N-Cbz-6-amino-5-chloronaphthalene-3-ylmethyl)-2-oxopyrrolidin-3-(\$)-yl]-(N-Cbz-6-amino-5-chloronaphthalene-3-ylmethyl)-2-oxopyrrolidin-3-(\$)-yl]-(N-Cbz-6-amino-5-chl

C. 2-[I1-(5-Cyanothiophene-3-ylmethyl)-2-oxopyrrolidin-3-(S)-yl)-(N-Cbz-6-amino-5-chloronaphthalene-2-sulfonyl)amino]acetamide

The title compound is prepared as described in EXAMPLE 127 Part C using 2-l[1-(5-cyanothiophene-3-ylmethyl)-2-oxopyrrolidin-3-(S)-yl]-(N-Cbz-6-amino-5-chloronaphthalene-2-sulfonyl)amino]acetic acid in place of 2-[[1-(5-cyanothiophene-3-ylmethyl)-2-oxopyrrolidin-3-(S)-yl]-(7-methoxynaphthalene-2-sulfonyl)amino]acetic acid. The crude product is purified by column chromatography eluting in a gradient of 50% EtOAc/CH₂Cl₂ to 2% MeOH/50% EtOAc/CH₂Cl₂ to provide the title compound as a solid.

EtOAc/CH₂Cl₂ to provide the title compound as a solid.

EtOAc/CH₂Cl₃ 300 MHz) δ 8.63 (d.-1H), 8.46 (s, 1H), 8.30 (d, 1H), 8.04 (d, 1H), 7.93 (d, 1H), 7.86 (s, 1H), 7.60 (s, 1H), 7.54 (m, 2H), 7.42 (m, 5H), 5.37 (s, 1H), 5.27 (s, 2H), 4.52 (m, 1H), 4.50 (AB, 2H), 3.78 (AB, 2H), 3.42 (m, 1H), 3.32 (m, 1H), 2.50 (m, 1H), 2.35 (m, 1H).

D. 2-[[1-(5-Carbamimidoylthiophene-3-ylmethyl)-2-oxopyrrolidin-3-(S)-yl]-(6-amino-5-chloronaphthalene-2-sulfonyl)amino]acetamide trifluoroacetate.

2-[[1-(5-Cyanothiophene-3-ylmethyl)-2-oxopyrrolidin-3-(S)-yl]-(N-Cbz-6-amino-5-chloronaphthalene-2-sulfonyl)amino]acetamide is converted to the title compound as described in EXAMPLE-125; Part D. The crude product is purified by RP-HPLC eluting in a gradient of 10% CH₃CN/H₂O (0.1% TFA) to 60% CH₃CN/H₂O (0.1% TFA) and the appropriate product fractions are lyophilized to provide the title compound as a white solid.

1 H NMR (DMSO-d₆, 300 MHz) δ 9.25 (bs, 2H), 8.95 (bs, 2H), 8.32 (s, 1H), 7.93 (d, 1H), 7.91 (s, 1H), 7.86 (d, 1H), 7.80 (m, 2H), 7.56 (s, 1H), 7.22 (m, 2H), 6.28

(bs, 2H), 4.75 (m, 1H), 4.34 (AB, 2H), 3.62 (AB, 2H), 3.16 (m, 2H), 2.07 (m, 1H), 1.95 (m, 1H). FAB MS, [M+H]*=615.

EXAMPLE 147

- 5 4-[3-(S)-(6-Aminonaphthalene-2-sulfonylamino)-2-oxopyrrolidin-1-ylmethyl]thiophene-2-carboxamidine dihydrochloride.
 - A. N-Cbz-6-aminonaphthalene-2-sulfonic acid-[1-(5-cyanothiophen-3-ylmethyl)-2-oxopyrrolidin-3-(S)-yl]amide.
- The title compound is prepared from 4-(3-(S)-amino-2-oxopyrrolidin-1-ylmethyl)thiophene-2-carbonitrile hydrochloride as described in EXAMPLE 125, Part C using N-Cbz-6-aminonaphthalene-2-sulfonyl chloride in place of 7-methoxynaphthalene-2-sulfonyl chloride. The crude product is purified by column chromatography eluting with a gradient of 10% EtOAc/CH₂Cl₂ to 25%
- EtOAc/CH₂Cl₂ to provide the title compound as a solid.

 ¹H NMR (CDCl₃, 300 MHz) δ 8.34 (s, 1H), 8.04 (s, 1H), 7.80 (d, 1H), 7.77 (d, 1H), 7.70 (d, 1H), 7.50 (s, 1H), 7.47 (d, 1H), 7.40 (m, 7H), 5.98 (d, 1H), 5.23 (s, 2H), 4.40 (AB, 2H), 3.82 (m, 1H), 3.25 (m, 2H), 2.58 (m, 1H), 2.08 (m, 1H).
- B. 4-[3-(S)-(6-Aminonaphthalene-2-sulfonylamino)-2-oxopyrrolidin-1ylmethyl]-thiophene-2-carboxamidine dihydrochloride.
 N-Cbz-6-aminonaphthalene-2-sulfonic acid-[1-(5-cyanothiophen-3-ylmethyl)2-oxopyrrolidin-3-(S)-yl]amide is converted to the title compound as described in EXAMPLE 125; Part D. The crude product is purified by RP-HPLC eluting in a gradient of 10% CH₃CN/H₂O to 80% CH₃CN/H₂O and the appropriate product
- fractions are lyophilized to provide the title compound as a white solid.

 H NMR (DMSO-d₆/300 MHz) δ 9:32 (bs, 2H), 8:99 (bs, 2H), 8:15 (s, 1H), 7.99 (d, 1H), 7.86 (m, 2H), 7.76 (d, 1H), 7.62 (m, 2H), 7.03 (dd, 1H), 6.86 (s, 1H), 4.35 (AB, 2H), 4.03 (m, 1H), 3:10 (m, 2H), 1:90 (m, 1H), 1:53 (m, 1H). FAB MS,

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30(a) [M+H](=444.h) in the constant blue constants series and equipment of the

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A. 7-Methoxynaphthalene-2-sulfonic acid [1-(5-cyanothiophen-2-ylmethyl)-2-oxopyrrolidin-3-(S)-yl]amide.

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The title compound is prepared as in EXAMPLE 125; Part Clusing 5-(3-amino-2-oxopyrrolidine-1-ylmethyl)thiophene-2-carbonitrile hydrochloride, prepared as in EXAMPLE 123, in place of 4-(3-amino-2-oxopyrrolidine-1ylmethyl)thiophene-2-carbonitrile hydrochloride. The crude product is surified by column chromatography eluting with gradient of 10%-EtOAc/CH, Cl, to 20% EtOAc/ CH2Cl2 to afford the title compound as a white solid red solid ¹H NMR (CDCl₃, 300 MHz) δ 8.36 (s, 1H), 7.89 (d, 1H), 7.75 (m, 2H), 7.43 (d, s. 1H), 7.30 (m, 1H), 7.22 (m, 2H), 6.90 (d, 1H), 5.44 (bs, 1H), 4.59 (AB, 2H), 3.90 (s, 3H), 3.74 (m, 1H), 3.28 (m, 2H); 2.61 (m, 1H), 2.10 (m, 1H). The little comprund is prepared from 4-(3-(3-)-amino-2-oxupy, rolidic B. 5-[3-(S)-(7-Methoxynaphthalene-2-sulfonylamino)-2-oxopyrrolidin-1vimethylithiophene-2-carboxamidine trifluoroacetate and the last 7-Methoxynaphthalene-2-sulfonic acid-[1-(5-cyanothiophen-2-ylmethyl)-2oxopyrrolidin-3-(S)-yl]amide is converted to the title compound as described in EXAMPLE 125, Part D. The crude product is purified by RP-HPLC eluting in a (0.1% TFA) and the appropriate product fractions are lyophilized to provide the title compound as a white solid: 32.3 (HE, 27), 3.85 (m, 1H), 3.85 (m; 51H) 2.55 (ME, 27), 4.65 ¹H NMR (CD₃OD, 300 MHz) δ 8.41 (s,1H), 7.96 (d,1H), 7.87 (d, 1H), 7.74 (m, 1H), 7.40 (d, 1H), 7.31 (dd, 1H), 7.18 (d, 1H), 4.64 (s, 2H), 4.10 (t, 1H), 3.91 (s, 3H), 3.28 (m, 2H), 2.21 (m, 1H), 1.76 (m, 1H). FAB MS, [M+H] = 459. d-Ober Coming naphhatana C-siftonic, apind siGoyanothiophala Swigns due and a sec of my begins only end as patientials at edited by (8)-6-nibitom known is 5-{3-(S)-[(7-Methoxynaphthalene-2-sulfonyl)methylamino]-2-oxopyrrolidin-1-25 ylmethyllthiophene-2-carboxamidine trifluoroacetate (1) in turnsaty s be thens are typohilized to provide the title compound as a white solid. A. 7-Methoxynaphthalene-2-sulfonic acid [1-(5-cyanothiophen-2-vlmethyl)-2oxopyrrolidin-3-(S)-yl]-methylamide. (1, b) 57.1 (3-7.5) (3-7.5) The title compound is prepared as in EXAMPLE 126, Part A using the 7-methoxynaphthalene-2-sulfonic acid [1-(5-cyanothiophen-2-ylmethyl)-2oxopyrrolidin-3-(S)-yl]amide, prepared as in EXAMPLE 148, Part A, in place of 7-methoxynaphthalene-2-sulfonic acid [1-(5-cyanothiophen-3-ylmethyl)-2-

H NMR (CDCI₃, 300 MHz) δ 8.41 (s, 1H), 7.91 (d, 1H), 7.78 (dd, 2H), 7.46 (m, 1H), 7.25 (m, 3H), 6.93 (d, 1H), 4.91 (t, 1H), 4.60 (AB, 2H), 3.92 (s, 3H), 3.31 (m, 2H), 2.74 (s, 3H), 2.36 (m, 1H), 2.03 (m, 1H). (Also before the large transfer of the la

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oxopyrrolidin-3-(S)-yl]amide. otograficontelleribioecoxont-iv-71-coi-61-3

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To a solution of 7-methoxynaphthalene-2-sulfonic acid [1-(5-cyanothiophen-3-ylmethyl)-2-oxopyrrolidin-3-(S)-yl]methylamide (0.48 g, 1 mmol) in 10 mL of EtOH is added hydroxylamine hydrochloride (0.11 g, 1.54 mmol) and triethyl amine (0.25 g, 2.5 mmol). The solution is heated to reflux. After 1 hour, the solution is concentrated. The crude product is purified by RP-HPLC eluting in a gradient of 10% CH₃CN/H₂O (0.1% TFA) to 80% CH₃CN/H₂O (0.1% TFA) and the appropriate product fractions are lyophilized to provide the title compound as a white solid.

¹H NMR (CDCl₃, 300 MHz) δ 8.49 (s, 1H), 7.84 (d, 1H), 7.76 (m, 2H), 7.60 (s, 1H), 7.35 (s, 1H), 7.28 (m, 1H), 7.20 (m, 1H), 6.75 (bs, 2H), 4.96 (t, 1H), 4.87 (bs, 1H), 4.40 (AB, 2H), 3.90 (s, 3H), 3.23 (m, 2H), 2.77 (s, 3H), 2.28 (m, 1H), 1.93 (m, 1H). FAB MS, [M+H]*= 489. Elemental analysis calculated with 1.75 mmol of H₂O cal. C=45.64%, H=4.53%, N=8.84%, found C=45.33%, H=4.05%, N=8.36%.

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EXAMPLE 153

2H), 2.31 (bs. 1H).

4-(3-(S)-Amino-2-oxopyrrolidin-1-ylmethyl)pyridine-2-carbonitrile trifluoroacetate.

A. 2-Cyano-4-[{(tert-butyldimethylsilyl)oxy}methyl]pyridine.

The title compound is prepared according to the procedure described in J.

Heterocyclic Chem. 30, 631 (1993). The crude residue obtained is purified by column chromatography eluting with gradient of 5% EtOAc/hexanes to 20%

EtOAc/hexanes to afford the title compound as a yellow oil.

¹H NMR (CDCl₃, 300 MHz) δ 8.66 (d, 1H), 7.69 (s, 1H), 7.48 (m, 1H), 4.80 (s, 2H), 1.00 (s, 9H), 0.19 (s, 6H).

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B. 2-Cyano-4-(hydroxymethyl)pyridine.

A solution of 2-cyano-4-[{(tèrt-butyldimethylsilyl)oxy}methyl]pyridine (10.1 g, 40.5 mmol) in 200 mL of anhydrous MeOH is stirred over 12 g of Dowex-50W-Ht ion-exchange resin (pre-washed with MeOH) for a period of 18 hours: After this time, the mixture is filtered and washed with MeOH twice. The combined filtrates are concentrated in vacuo. The crude residue is purified by column chromatography eluting with 50% EtOAc/hexanes to afford the title compound (4.82 g, 35.9 mmol) as an oil.

14 NMR (CDCl₃, 300 MHz) δ 8.70 (m, 1H), 7.75 (s, 1H), 7.55 (d, 1H), 4.87 (d,

(Mr. (ad)) 20 0 10 10

To a solution of 7-methoxynaphthalana-2-suitonic acid [17/5-event incom-2to be C. 2-Cyano-4-(bromomethyl)pyridines; anibilionygoxo-2-(iyrdamiy Modern Bromine (6.88 g, 43.1 mmol) is added dropwise to a solution of OB triphenylphosphine (11.3 g, 43.1 mmol) in 280 mL of CH, ClCat 0°Cs The 5 mixture is tirred for 30 minutes at 0°C. At this time, 2-cyano-4-(hydroxymethyl)pyridine (4.82 g. 35.9 mmol) is added and the resulting mixture is stirred for 2 hours at room temperature. The reaction mixture is diluted with CH, Cl, and washed with water (2x) and saturated NaCl solution. The organic layer is dried with MgSO4, filtered and concentrated. The crude product is purified by column 10 chromatography eluting in a gradient of 20% EtOAc/hexanes to 30% EtOAc/hexanes to afford the title compound (6.40 g./32.5 mmol) as an oil. 31. H NMR (CDCI₃, 300 MHz) & 8.75 (d, 1H), 7.79 (s, 1H); 7.60 (d, 1H); 4.49 (s, 2H). Calculate and the control of the contro H=4.05%, N=5.36%. D. [1-(2-Cyano-pyridin-4-ylmethyl)-2-oxopyrrolidin-3-(S)-yl]carbamic acid tert-15 butyl ester. EXAMPLE 153 The title compound is prepared from (2-oxopyrrolidin-3-(S)-yl)-carbamic acid tert-butyl ester as described in EXAMPLE 122, Part F using 2-cyano-4-(bromomethyl)pyridine in place of 4-bromomethylthiophene-2-carbonitrile. The 20 crude product is purified by column chromatography eluting with gradient of 25% EtOAc/CH2Cl2 to 50% EtOAc/CH2Cl2 to afford the title compound as a tleteropyclic (mam, 30, 631 (1093). The enuce residue obtained is furthed H NMR (CDCI, 300 MHz) & 8.69 (d, 1H), 7.70 (s, 1H), 7.46 (d, 1H), 5:42 (bs, 1H), 4.57 (AB, 2H), 4.22 (m, 1H), 3.35 (m, 2H), 2.62 (m; 1H), 2.10 (m; 1H), 1.50 25 (s, 9H), (CDC 4, 300 MHz) 5 8.60 (d 114), 7.64 (m; (He , a), 7.48 (m; (He , a), 20.05) 2H), 1.00 (s, 9H), 0.19 (s, 6H). E. 4-(3-(S)-Amino-2-oxopyrrolidin-1-vlmethyl)pyridine-2-carbonitrile trifluoroacetate. B. 2-Owng-4-(bydenxymethyl)cyridins To a solution of [1-(2-cyano-pyridin-4-ylmethyl)-2-oxopyrrolidin-3-(S)-4 yl]carbamic acid ten-butyl ester (3.34,g, 10.6 mmol) in 50 mL of CH₂Cl₂ is OS added 5 mL of TFA. The reaction mixture is stirred for 18 hours and then concentrated to give the title compound (3.40 g, 10.3 mmol) as a white train. ¹H NMR (DMSO-d₆, 300 MHz) δ,7,90 (d, 1H), 7.70 (bs.,3H), 7.09 (s, 1H), 6.80 (m, 1H), 3.78 (AB, 2H), 3.35 (m, 1H), 2.55 (m, 2H), 1.62 (m, 1H); 1.20 (m, 1H). (4.82 g, 66.9 mmch as an oil.) O 18 O 18 LO 200 MP) 8 8.70 (m. 18) 1.77 (H 1 m) 201 MP GOS (LOCA) FAM H

ABOUT AUST

- B. 5-{3-(\$)-[(7-Methoxynaphthalene-2-sulfonyl)methylamino]-2-oxopyrrolidin-1-ylmethyl}thiophene-2-carboxamidine trifluoroacetate.
- 7-Methoxynaphthalene-2-sulfonic acid [1-(5-cyanothiophen-2-ylmethyl)-2-oxopyrrolidin-3-(S)-yl]methylamide is converted to the title compound as
- described in EXAMPLE 125, Part D. The crude product is purified by RP-HPLC eluting in a gradient of 10% CH₃CN/H₂O (0.1% TFA) to 80% CH₃CN/H₂O (0.1% TFA) and the appropriate product fractions are lyophilized to provide the title compound as a white solid.

¹H NMR (DMSO-d₆, 300 MHz) δ 9.20 (bs, 2H), 8.82 (bs, 2H), 8.38 (s, 1H), 8.04 (d, 1H), 7.96 (d, 1H), 7.83 (d, 1H), 7.69 (dd, 1H), 7.57 (d, 1H), 7.34 (dd, 1H), 7.21 (d, 1H), 4.83 (t, 1H), 4.61 (AB, 2H), 3.89 (s, 3H), 3.19 (m, 2H), 2.62 (s, 3H), 2.04 (m, 1H), 1.82 (m, 1H). FAB MS, [M+H][†]=473.

EXAMPLE 150 Cost and the accompany of the Source Post of

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15 <u>5-(3-(S)-[(7-Methoxynaphthalene-2-sulfonyl)benzylamino]-2-oxopyrrolldin-1-ylmethyl)thiophene-2-carboxamidine_trifluoroacetate:</u>

THE WEST OF THE PROPERTY OF SE

- A. 7-Methoxynaphthalene-2-sulfonic acid [1-(5-cyanothiophen-2-ylmethyl)-2-oxopyrrolidin-3-(\$)-yl]- benzylamide.
- The title compound is prepared as in EXAMPLE 126, Part A using 7-methoxynaphthalene-2-sulfonic acid[1-(5-cyanothiophen-2-ylmethyl)-2-oxopyrrolidin-3-(S)-yl]amide, prepared as in EXAMPLE 148, Part A, in place of 7-methoxynaphthalene-2-sulfonic acid [1-(5-cyanothiophen-3-ylmethyl)-2-oxopyrrolidin-3-(S)-yl]amide and benzyl bromide for methyl iodide.
- 25 H, NMR, (CDCl₃, 300 MHz) δ 8.43 (s, 1H), 7.92 (m, 2H), 7:80 (d, 1H), 7.47 (m, 1H), 7.31 (m, 3H), 7.22 (m, 4H); 6.93 (d, 1H), 4.55 (m, 4H); 4.26 (m, 1H), 3.93 (s, 3H), 3.12 (m, 2H), 2.28 (m, 1H); 1.96 (m, 1H). (Fit m) δθ. (π, 2H)
 - B. 5-{3-(S)-[(7-Methoxynaphthalene-2-sulfonyl)benzylamino]-2-oxopyrrolidin-1-ylmethyl}thiophene-2-carboxamidine trifluoroacetate.
 - 7-Methoxynaphthalene-2-sulfonic acid [1-(5-cyanothiophen-2-ylmethyl)-2-oxopyrrolidin-3-(S)-yl]- benzylamide is converted to the title compound as described in EXAMPLE 125. Part D. The crude product is purified by RP-HPLC eluting in a gradient of 10% CH₃CN/H₂O (0.1% TFA) to 80% CH₃CN/H₂O (0.1%
 - 35 TFA) and the appropriate product fractions are lyophilized to provide the title compound as a white solid as the solid was a white solid as the solid was the solid as the

 $\mathcal{C}(C,\mathcal{C})$

¹H.NMR (DMSO-d_s, 300 MHz) δ 9.22 (bs, 2H), 9.05 (bs, 2H), 8.42 (s. 1H), 8.05 (d, 1H), 7.96 (d, 1H), 7.88 (d, 1H), 7.80 (m, 1H), 7.53 (s, 1H), 7.28 (m, 6H), 7.15 ~ (Fell-(d) 1H), 4.72 (t, 1H); 4.52 (m, 3H), 4.19 (m, 1H); 3.88 (s, 3H); 3.14 (m, 1H), 3.05 = (m̃,1H), 2.13 (m, 1H), 1.74 (m, 1H) FAB MS, [M+H] = 549 10 1 (qoxo วงเลือ EXAMPLE 125 Part D The account is purified by เฮ เล eluting in a pancient of 10% GHyOng CO TEA) 12F (15) 12F AMPLE 130 (0.1% IAmino-(4-(3-(S)-(7-methoxynaphthalene-2-sulfonyl)meth oxopyrrolidin-1-ylmethyl)thiophene-2-yl)methylenejcarbamic acid methyl ester trifluoroacetate! SCR (HS SCIOS B B COMM SCR SCIOR AT MANNET (리마터) 기타 (d, 1원, 기타 3 (c. 1원) 라 (dd, 1원) 7.57 (d 마다) 7.31 c A. [Amino-(4-(3-(S)-(7-methoxynaphthalene-2-sulfonyl)methylamino]-2oxopyrrolidin-1-ylmethylithiophene-2-yl)methylenejcarbamic acid methyl ester trifluoroacetate. To a solution of 4-{3-(S)-[(7-methoxynaphthalene-2-sulfonyl)methylamino]-2-15/2 oxopyrrölidin-1-ylmethyl}thiophene-2-carboxamidine trifluoroacetate (0.7 g, 1.20 mmol) in 12 mL of CH2Cl2 and 1 mL of DMF at 0°C is added N-methyl piperidine(0.42 g, 4.2 mmol) and methyl chloroformate (0.12 g, 1.26 mmol). After 0.5 hour, the solution is diluted EtOAc. The organic solution is washed with H₂O and sat. NaCl. The organic layer is dried over MgSO₄, filtered and concentrated. The crude product is purified by RP-HPLC eluting in a gradient 20 of 10% CH₃CN/H₂O (0.1% TFA) to 80% CH₃CN/H₂O (0.1% TFA) and the appropriate product fractions are lyophilized to provide the title compound as a on the white solid dominance of [telephone policy in phthair contains and the contains and ¹H NMR (DMSO-d₆, 300 MHz) δ 9.58 (bs, 2H) 8.39 (s, 1H), 8.05 (d, 1H), 7.96 25 (d, 1H), 7.82 (d, 1H), 7.74 (s, 1H), 7.68 (d, 1H), 7.58 (d, 1H), 7.35 (dd, 1H), 7.15 (d, 1H), 4.86 (t, 1H), 4.32 (AB, 2H), 3.86 (s, 3H), 3.66 (s, 3H), 3.13 (m, 2H), 2.64 (s, 3H), 1.96 (m, 1H), 1.71 (m, 1H). FAB MS, [M+H] = 531. Elemental analysis calculated with 1.75 mmol of H₂O cal. C=46.22%, H=4.54%, N=8.29%, found 1947、11.C=46.00%(H=4.02%(N=7.93%)的现象过程以及,2010(M-XV) 131-313 1.5 30 elasaco oppin enibiro con de l'energaciphi di bemix i

EXAMPLE 152 incorve to a place cinotics the result departs of the A-(3-(S)-[(7-Methoxynaphthalene-2-sulfonyl)methylamino]-2-0x0pyřřólidin-1-14-54 : ylmethyl)thiophene-2-N-hydroxycarboxamidine-třítiuoroacetate: 1000b

35 A. 4-(3-(S)-[(7-Methoxynaphthalene-2-sulfonyl)methylâmino]-2-oxopyrrolidin-1-ylmethyl}thiophene-2-N-hydroxycarboxamidine trifluoroacetate:

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4-[3-(S)-(7-Methoxynaphthalene-2-sulfonylamino)-2-oxopyrrolidin-1-ylmethyl]-pyridine-2-carboxamidine trifluoroacetate.

A. 7-Methoxynaphthalene-2-sulfonic acid-[1-(2-cyanopyridin-4-ylmethyl)-2-

- The title compound is prepared as described in EXAMPLE 125, Part C using 4-(3-(S)-amino-2-oxopyrrolidin-1-ylmethyl)pyridine-2-carbonitrile trifluoroacetate in place of 4-(3-(S)-amino-2-oxopyrrolidine-1-ylmethyl)thiophene-2-carbonitrile hydrochloride. The crude product is purified by column chromatography
- eluting with a gradient of 25% EtOAc/CH₂Cl₂ to 50% EtOAc/CH₂Cl₂ to provide the title compound as a white solid. Inotite section of the solid. In the
 - B. 4-[3-(S)-(7-Methoxynaphthalene-2-sulfonylamino)-2-oxopyrrolidin-1ylmethyl]pyridine-2-carboxamidine trifluoroacetate.

 Hydrogen sulfide gas is bubbled for 5 minutes through a solution of 7methoxynaphthalene-2-sulfonic acid-[1-(2-cyanopyridin-4-ylmethyl)-2-
- 20 oxopyrrolidin-3-(S)-yl]amide (0.22 g, 0.50 mmol) in 10 mL of a 10:1 mixture of pyridine/triethylamine. After stirring the pale green solution for a period of 18 hours, the reaction mixture is concentrated in vacuo. The residue is diluted in acetone and concentrated to give the crude thioamide. To a solution of thioamide in 10 mL of acetone is added lodomethane (1 mL 16 mmol). The
- resulting mixture is heated at reflux for 1 hour, allowed to cool to room temperature and concentrated in vacuo to provide the crude thiolimidate hydroiodide. To a solution of thiolimidate hydroiodide in 10 mL of MeOH is added ammonium acetate (0.15 g; 1.9 mmol). The resulting mixture is heated at reflux for 2 hours, allowed to cool to room temperature and stirred overnight.
 - 30 The resulting mixture is concentrated in Vacuo to provide the crude amidine salt. The crude product is purified by RP-HPLC eluting in a gradient of 15% CH₃CN/H₂O (0.1% TFA) to 80% CH₃CN/H₂O (0.1% TFA) and the appropriate product fractions are lyophilized to provide the title compound (0.10 g, 0.18 mmol) as a white amorphous solids and appropriate common as a white amorphous solids.
 - ¹H NMR (DMSO-d_s, 300:MHz): 8 9.51 (bs; 2H); 9.40 (bs; 2H); 8.73 (d; 1H), 8.37 (s,1H), 8.25 (d, 1H), 8.02 (d, 1H), 7.92 (m, 2H), 7.72 (dd, 1H), 7.58 (d, 1H), 7.53

<u>Hiv.tremt. (si.1H), 7.32 (dd, 1H); 4.49 (AB, 2H); 4.18 (m; 1H); 3.86 (s, 3H); 3.15 (m, 2H),</u> 2.02 (m, 1H), 1.64 (m, 1H)<u>s;FAB:MS, (M+H)</u> ±454s (od to : S entitivo

A 7-Methoxynaphthalene-2-sulfonio acid-[1-(2-cyar66ty=1,9MAX=1,thyl)-2-4-(3-(S)-[(7-Methoxynaphthalene-2-sulfonyl)benzvlaminol-2-oxopyrrolidin-1-The true compounds to the true compound the true compound of the true compounds and the true compounds the true compound the tr (3-(S)-2mnio-2-oxcoyrrolidin-1-ylmethyl)pyridine-2-carbonitrile trifluorcacetate elidine dias A. 7-Methoxynaphthalene-2-sulfonic acid-[1-(2-cvanopyridin-4-vimethyl)-2hydrochlande. The crude produ**eblmslyzned-[ly-(S)-E-nibilonayqoxo**apha 1.00 oThe title compound is prepared as described in EXAMPLE:141; Part D using 7-methoxynaphthalene-2-sulfonic acid-[1-(2-cyanopyridin-4-ylmethyl)-2m) 35 oxopyrrolidin-3-(S)-yllamide in place of N-Cbz-7-aminonaphtháléné-2-sulfonic acid-[1-(5-cyanothiophen-3-ylmethyl)-2-oxopyrrolidin-3-(S)-yl]amide? The HI micrude product is purified by column chromatography eluting with gradient of CH₂Cl₂ to 3% MeOH/CH₂Cl₂ to afford the title compound as a white solid. H.NMR. (CDCI. 300 MHz) 8.866 (d. 1H); 8:48 (s; 1H), 7.98 (m) 2H), 7.80 (d. 1H), 7.53 (s, 1H), 7.41_c(d, 1H), 7.29 (m; 7H), 4.47 (AB, 2H), 4.45 (AB, 2H), 4.45 . (m, 1H), 3.94 (s, 3H), 3.11 (m, 2H), 2:30 (m, 1H), 2:19 (m) 1H) 201by 1 methoxynaphthalene-2-sulfonic acid-[1-(2-cyanopyridin-4-yimethyi)-2-20 x B. 4-(3-(S)-[(7-Methoxynaphthalene-2-sulfonyl)beńżylaminol-2-oxopyrrolidin-31 to no 1-ylmethyl)pyridine-2-carboxamidine trifluoroacetate slyritein saribhyd of hearth 7-Methoxynaphthalene-2-sulfonic acid [1-(2-cyanopyridin-4-ylmethyl)-2oxopyrrolidin-3-(S)-yl]-benzylamide is converted to the title compound as described in EXAMPLE, 154, Part B. The crude product is purified by RP-HPLC eluting in a gradient of 10% CH₃CN/H₂O (0.1% TFA) to 80% CH₃CN/H₂O (0.1% TFA) and the appropriate product fractions are lyophilized to provide the title hydroicdide. To a solution of thioimidate ibilosipility as a bruogmooth is H NMR (DMSO-d_{e-3}300 MHz) δ₃9.50 (bs. 2H), 9.29 (bs. 2H), 8.75 (d, 1H), 8.48 January (s,1H), 8.02 (d,1H), 7.96 (d,1H), 7.93 (s,1H), 7.83 (dd,1H), 7.56 (m,2H), 7.35 ҇҉30₋₋₋₋₋(m, 3H), 7,29<u>-(m, 3H), 4,84 (m, 1H), 4,44</u> (AB_D2H), 4,42 (AB, 2H); 3.90′(s, 3H), 3.20 (m, 1H), 3.05 (m, 1H), 2.19 (m, 1H), 1.80 (m, 1H). FAB MS, [M+H] =544. CH₀CN,H₂O (0.1% TFA) to 80% CH₂ON/H₂O (0.1% TFA) and the appropriate product traditions are lyaphilized to provide the title continuous are should be a should 4-(3-(S)-[(7-Methoxynaphthalene-2-sulfonyl)methylamino]-2-oxopyrrolidin-1-35 (J. vlmethyl)pyridine-2-carboxamidine-trifluoroacetate, p-OBMC, RMM HE (a, (H), 6,25 (c, 1H), 8 02 (d, 1H), 7.92 (m, 2H), 7.72 (dd 7.H), 7 58 (d, (H), 7 5),

A. 7-Methoxynaphthalene-2-sulfonic acid-[1-(2-cyanopyridin-4-ylmethyl)-2-oxopyrrolidin-3-(S)-yl]-methylamide.

The title compound is prepared from 7-methoxynaphthalene-2-sulfonic acid-[1-(2-cyanopyridin-4-ylmethyl)-2-oxopyrrolidin-3-(S)-yl]amide as described in

5 EXAMPLE 141, Part D using methyl iodide in place of benzyl bromide. The crude product is purified by column chromatography eluting with gradient of 20% EtOAc/CH₂Cl₂ to 40% EtOAc/CH₂Cl₂ to afford the title compound as a white solid.

¹H NMR (CDCl₃, 300 MHz) δ 8.65 (d, 1H), 8.41 (s, 1H), 7.90 (d, 1H), 7.79 (m, 2H), 7.53 (s, 1H), 7.37 (m, 1H), 7.00 (m, 2H), 4.57 (m, 1H), 7.70 (m, 2H), 7.53 (s, 1H), 7.37 (m, 1H), 7.00 (m, 2H), 4.57 (m, 2H),

10 2H), 7.53 (s, 1H), 7.37 (m, 1H), 7.29 (m, 2H), 4.97 (m, 1H), 4.47 (AB, 2H), 3.93 (s, 3H), 3.29 (m, 2H), 2.83 (s, 3H), 2.40 (m, 1H), 2.10 (m, 1H).

B. 4-{3-(S)-[(7-Methoxynaphthalene-2-sulfonyl)methylamino]-2-oxopyrrolidin-1-ylmethyl)pyridine-2-carboxamidine trifluoroacetate.

7-Methoxynaphthalene-2-sulfonic acid-[1-(2-cyanopyridin-4-ylmethyl)-2-oxopyrrolidin-3-(S)-yl]methylamide is converted to the title compound as described in EXAMPLE 154, Part B. The crude product is purified by RP-HPLC eluting in a gradient of 10% CH₃CN/H₂O (0.1% TFA) to 80% CH₃CN/H₂O (0.1% TFA) and the appropriate product fractions are lyophilized to provide the title compound as a white solid.

¹H NMR (DMSO-d_s, 300 MHz) δ 9.54 (bs, 2H), 9.31 (bs, 2H), 8.74 (d, 1H), 8.40 (s,1H), 8.04 (d, 1H), 7.97 (s, 1H), 7.95 (d, 1H), 7.70 (dd, 1H), 7.59 (m, 2H), 7.37 (m, 1H), 4.99 (m, 1H), 4.50 (AB, 2H), 3.89 (s, 3H), 3.24 (m, 2H), 2.71 (s, 3H), 2.05 (m, 1H), 1.88 (m, 1H). FAB MS, [M+H] $^{+}$ =468.

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EXAMPLE 157

4-[3-(S)-(5-Chloro-3-methylbenzo[b]thlophene-2-sulfonylamino)-2c export of the sulfation of the sulfation

A 5-Chloro-3-methylbenzo[b]thiophene-2-sulfonic acid [1-(2-cyanopyridin-4 ylmethyl)-2-oxopyrrolidin-3-(S)-yllamide.

The title compound is prepared as described in EXAMPLE 125, Part C using 4-(3-(S)-amino-2-oxopyrrolidin-1-ylmethyl)pyridine-2-carbonitrile trifluoroacetate in place of 4-(3-(S)-amino-2-oxopyrrolidine-1-ylmethyl)-thiophene-2-carbonitrile hydrochloride and with 5-chloro-3-methylbenzo[b]thiophene-2-sulfonyl chloride in place of 7-methoxynaphthalene-2-sulfonyl chloride. The crude product is purified by column chromatography

eluting with gradient of 25% EtOAc/CH2Cl2 to 50% EtOAc/CH2Cl2 to afford the title compound as a white solid. <u>as malydiam-light?)-E nibitanyqoxo</u> ¹H NMR (CDCI₂, 300 MHz) δ 8.67 (d, 1H), 7.82 (s, 1H), 7.76 (d, 1H), 7.51 (s, 1H), 7.48 (gd, 1H), 7.32 (d, 1H), 5.65 (d; 1H), 4.49 (AB; 2H), 4.00 (m; 1H), 3.29 (m, 2H), 2.71 (s, 3H), 2.66 (m, 1H), 2.19 (m, 1H). had in A. MAXE theibarg this chitule ydgargotamonilo nutilios yd beiling si 'ouborg abure B. 4-[3-(S)-(5-Chloro-3-methylbenzo[b]thlophene-2-sulfonylamino)-2oxopyrrolidin-1-ylmethyl]pyridine-2-carboxamidine trifluoroacetateida 5-Chloro-3-methylbenzo[b]thiophene-2-sulfonic acid [1-(2-cyano-pyridin-4ylmethyl)-2-oxopyrrolidin-3-(S)-yl]amide is converted to the title compound as described in EXAMPLE, 154, Rart B. (The crude product is purified by RP-HPLC eluting in a gradient of 10% CH₃CN/H₂O (0.1% TFA) to 80% CH₃CN/H₂O (0.1% TFA) and the appropriate product fractions are lyophilized to provide the title compound as a white solid. until enibimaxod to S-anibimativemiy-t 1H NMR (DMSO-d_s, 300 MHz) δ, 9.51 (bs, 2H), 9.42 (bs, 2H), 8.78 (d/-11-), 8.76 (s,1H), 8.09 (d, 1H), 8.05 (s, 1H), 7.94 (s, 1H), 7.59 (s, 1H), 7.57 (d, 1H), 4.50 FAB MS, [M+H] =478.- Elemental analysis calculated with 1.4 mole of H₂O: C=42.81%, H=3.89%, N=11.35%; found C=42.82%; H=3.30% N=10.84%. 20 : empound as a white solid. EXAMPLE 158 .80) 18.4 (HS.46) 48.6 (IHM OUR .H-OSMO) HMM H 4-{3-(\$)-[(5-Chloro-3-methylbenzo[b]thiophene-2-sulfonyl)methylamino]-2oxopyrrolidin-1-ylmethyl)pyridine-2-carboxamidine trifluoroacetate. (m) 2.05 (a), 1H), 1.36 (m, 1H), FAB MS MAHH = 458 A. 5-Chloro-3-methylbenzo[b]thiophene-2-sulfonic acid [1-(2-cyanopyridin-4-25 vlmethyl)-2-oxopyrrolidin-3-(S)-yl]-methylamide. The title compound is prepared from 5-chloro-3-methylbenzo[b]thiophene-2sulfonic acid [1-(2-cyanopyridin-4-ylmethyl)-2-oxopyrrolidin-3-(S)-yl]amide as described in EXAMPLE 141, Part D using methyl lodide in place of benzyl bromide. The crude product is purified by column chromatography eluting with 30 gradient of 10% EtOAc/CH2Cl2 to 25% EtOAc/CH2Cl2 to afford the title compound as a white solid. bedins as described with an incompound is prepared as described with a solid soli ¹H NMR (CDCl₃, 300 MHz) δ 8.66 (d, 1H), 7.80 (s, 1H), 7.74 (d, 1H), 7.53 (s, 1H), 7.43 (dd, 1H), 7.35 (d, 1H), 4.95 (m, 1H), 4.47 (AB, 2H), 3.29 (m, 2H); 2.91 (s; 3H), 2.70 (s, 3H), 2.41 (m, 1H), 2.15 (m, 1H), 1 classed as Senerge in 35 binzoful hispheni Paulionyl oblande in place of Signalius, 243, thoration

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B. 4-(3-(S)-[(5-Chloro-3-methylbenzo[b]thiophene-2-sulfonyl)methylamino]-2-oxopyrrolidin-1-ylmethyl]pyridine-2-carboxamidine trifluoroacetate.

5-Chloro-3-methylbenzo[b]thiophene-2-sulfonic acid-[1-(2-cyanopyridin-4-ylmethyl)-2-oxopyrrolidin-3-(S)-yl]methylamide is converted to the title compound as described in EXAMPLE 154, Part B. The crude product is purified by RP-HPLC eluting in a gradient of 10% CH₃CN/H₂O (0.1% TFA) to 80% CH₃CN/H₂O (0.1% TFA) and the appropriate product fractions are lyophilized to provide the title compound as a white solid.

14 NMR (DMSO-d₈, 300 MHz) § 9.52 (bs, 2H), 9.34 (bs, 2H), 8.74 (d, 1H), 8.08 (m, 2H), 7.95 (s, 1H), 7.63 (s, 1H), 7.61 (dd, 1H), 4.99 (m, 1H), 4.50 (AB, 2H), 3.31 (m, 1H), 3.21 (m, 1H), 2.80 (s, 3H), 2.66 (s, 3H), 2.14 (m, 1H), 2.03 (m, 1H). FAB MS, [M+H] = 493.

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EXAMPLE 159 HOLD STATE OF THE STATE OF THE PARTY.

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15 2-{[1-(2-CarbamimIdoylpyridine-4-ylmethyl)-2-oxopyrrolidin-3-(S)-yl]-(7-methoxynaphthalene-2-sulfonyl)amino}acetamide trifluoroacetate.

A. 2-[[1-(2-Cyanopyridine-4-ylmethyl)-2-oxopyrrolidin-3-(S)-yl]-(7-methoxynaphthalene-2-sulfonyl)aminolacetic acid *tert*-butyl ester.

The title compound is prepared from 7-methoxynaphthalene-2-sulfonic acid-[1-(2-cyano-pyridin-4-ylmethyl)-2-oxopyrrolidin-3-(S)-yl]amide as described in EXAMPLE 141, Part D using tert-butyl bromoacetate in place of benzyl bromide. The crude product is purified by column chromatography eluting with gradient of 10% EtOAc/CH₂Cl₂ to 25% EtOAc/CH₂Cl₂ to afford the title

compound as a white solid grae and box (ATT 300) Comp

¹H NMR (CDCl₃,300 MHz), δ 8.66 (d, 1H), 7.29 (dd, 1H), 7.90 (d, 1H), 7.85 (d, 1H), 7.79 (d, 1H), 7.58 (s, 1H), 7.42 (d, 1H), 7.29 (dd, 1H), 7.28 (m, 1H), 4.56 (m, 1H), 4.49 (AB, 2H), 3.99 (AB, 2H), 3.94 (s, 3H), 3.31 (m, 2H), 2.63 (m, 1H), 2.54 (m, 1H), 1.43 (s, 9H), 10.88 (Hz, 2), 65 (Hz

B. 2-[[1-(2-Cyanopyridine-4-ylmethyl)-2-oxopyrrolidin-3-(S)-yl]-(7-methoxynaphthalene-2-sulfonyl)amino]acetic acid. Oar HJ9(14-3).

2-[[1-(2-Cyanopyridine-4-ylmethyl)-2-oxopyrrolidin-3-(S)-yl]-(7-3-3).5
methoxynaphthalene-2-sulfonyl)amino]acetic acid: tert-butyl estertis converted to the title compound as described in EXAMPLE 127, Part B., The product is azeotroped with toluene to give a white foam.

. Σομέτου ¹H.NMR (CDCl₃, 300 MHz) δ 9.61 (bs, 1H), 8.70 (d, 1H), 8.39 (s, 1H), 7.90 (d. 1H), 7.79 (d, 1H), 7.70 (d, 1H), 7.68 (s, 1H), 7.51 (m, 1H), 7.30 (m, 1H), 7.20 (d. 1H), 4.80 (m; 1H), 4.59 (AB; 2H), 4.01 (s, 2H), 3.95 (s, 3H), 3.40 (m, 2H), 2.48 = (m; 1H), 2.31 (m; 1H). FAB MS; [M+H] =495. Blot was a standard compound is described in EXAMPLE 154, Part B. 18. coude product ic C. 2-[[1-(2-Cvanopyridine-4-vimethyl)-2-oxopyrrolidin-3-(S) methoxynaphthalene-2-sulfonyl)aminolacetamide. Cal The title compound is prepared as described in EXAMPLE 127, Part C using 2-[[1-(2-cyanopyridine-4-ylmethyl)-2-oxopyrrolidin-3-(S)-yl]-(7-10 methoxynaphthalene-2-sulfonyl)aminojacetic acid in place of 2-[[1-(5-He m) Cyanothiophene-3-ylmethyl)-2-oxopyrrolidin-3-(S)-yl]-(7-methoxynaphthalene-2-sulfonyl)amino)acetic acid. The crude product is concentrated from EtOAc to afford the title compound as a white solid. ¹H NMR (CDCl₃, 300 MHz) δ 8.73 (d, 1H), 8.40 (s, 1H), 7.91 (d, 1H), 7.80 (m, 15 2H), 7.69 (s, 1H), 7.50 (d, 1H), 7.32 (m, 1H), 7.29 (m, 1H), 5.45 (bs, 2H), 4.58 (m; 1H); 4.57 (AB, 2H); 3.98 (s; 3H); 3.82 (AB, 2H); 3.40 (m; 1H); 3.32 (m, 1H). 2.51 (m, 1H), 2.42 (m, 1H). マルドス・1名)・アンのは何かいなさる文字を行いて作品できた。中本印度は元はさいと大力での行行です。 マ D. 2-{[1-(2-Carbamimidov]-pvridine-4-vimethyl)-2-oxopvrrolidin-3-(\$)-vil-(7-20 methoxynaphthalene-2-sulfonyl)aminolacetamide trifluoroacetate 2-[[1-(2-Cyanopyridine-4-ylmethýl)-2-oxopyrrôlidin-3-(S)-yl]-(7-5\forall -3methoxynaphthalene-2-sulfonyl)áminojacétámide is converted to the title compound as described in EXAMPLE 154; Part B. The crude product is purified by RP-HPLC eluting in a gradient of 10% CH, CN/H, O (0.1% TFA) to 80% CH₂CN/H₂O (0.1% TFA) and the appropriate product fractions are 25 Provide the title compound as a white solid. 10.1 (c¹H NMR (DMSO-d₆)300 MHz) δ 9.52 (bs, 2H), 9.33 (bs, 2H), 8.75 (d, 1H), 8.45 \(s\)1H\);\(8.04\)(d, 1H);\(7.99\)(s\)(1H)\(7.95\)(d, 1H);\(7.77\)(d\)1H),\(7.64\)(d\)1H),\(7.58\) (bs, 2H), 7.35 (dd, 1H), 7.25 (s, 1H), 4.88 (m, 1H), 4.50 (AB, 2H), 3.90 (s, 3H), 3.73 (AB, 2H), 3.25 (m, 2H), 2.11 (m, 2H). FAB MS, [M+H]+=511. 30 -7]-W-(SES, pittlerrigexe-s-draftingly-besubhyeansy (-5)-Lib-bes

EXAMPLE 160 <u>Line of epotentials (by clue S-ensited opervations</u>

2-{[1-(2-Carbamimidoyl-pyridine-4-ylmethyl)-2-oxopyrrolidin-3-(S)-yl]-(7on the no methoxynaphthalene-2-sulfonyl)amino}-N-phenethylacetamide of the second operation operation

amnetications evip as sension of about attentis

- A. 2-[[1-(2-Cyanopyridine-4-ylmethyl)-2-oxopyrrolidin-3-(S)-yl]-(7-methoxynaphthalene-2-sulfonyl)amino]-N-phenethylacetamide.

 The title compound is prepared as described in EXAMPLE 127, Part C using 2-[[1-(2-cyan-pyridine-4-ylmethyl)-2-oxopyrrolidin-3-(S)-yl]-(7-methoxynaphthalene-2-sulfonyl)amino]acetic acid in place of 2-[[1-(5-cyanothiophene-
- naphthalene-2-sulfonyl)amino]acetic acid in place of 2-[[1-(5-cyanothiophene-3-ylmethyl)-2-oxopyrrolidin-3-(S)-yl]-(7-methoxynaphthalene-2-sulfonyl)aminoJacetic acid and with phenethylamine instead of NH₄OH. The crude product is purified by column chromatography eluting with gradient of 50% EtOAc/CH₂Cl₂ to 2% MeOH//50% EtOAc/CH₂Cl₂ to afford the title compound as a white solid.
- 10 ¹H NMR (CDCl₃, 300 MHz) δ 8.70 (d, 1H), 8.39 (s, 1H), 7.89 (d, 1H), 7.80 (d, 1H), 7.69 (s, 1H), 7.50 (d, 1H), 7.25 (m, 7H), 7.11 (d, 1H), 4.55 (AB, 2H), 4.31 (bs, 1H), 3.94 (m, 1H), 3.90 (s, 3H), 3.81 (AB, 2H), 3.38 (m, 2H), 3.26 (m, 2H), 2.65 (m, 2H), 2.35 (m, 1H), 1.85 (m, 1H).
- 15 B. 2-{[1-(2-Carbamimidoyl-pyridine-4-ylmethyl)-2-oxopyrrolidin-3-(S)-yl]-(7-methoxynaphthalene-2-sulfonyl)amino}-N-phenethylacetamide trifluoroacetate.
 - 2-[[1-(2-Cyanopyridine-4-ylmethyl)-2-oxopyrrolldin-3-(S)-yl]-(7-

THE TOTAL OF MICHOLINE OF PERSON OF THE

- methoxynaphthalene-2-sulfonyl)amino]-N-phenethylacetamide is converted to the title compound as described in EXAMPLE 154, Part B. The crude product is purified by RP-HPLC eluting in a gradient of 10% CH₃CN/H₂O (0.1% TFA) to 80% CH₃CN/H₂O (0.1% TFA) and the appropriate product fractions are lyophilized to provide the title compound as a white solid.
- 1H NMR (DMSO-d₆,300 MHz) δ 9.52 (bs, 2H), 9.37 (bs, 2H), 8.75 (d, 1H), 8.44
 25 (s, 1H), 8.19 (m, 1H), 8.03 (d, 1H), 7.99 (s, 1H), 7.97 (d, 1H), 7.77 (dd, 1H), 7.65 (d, 1H), 7.57 (s, 1H), 7.36 (dd, 1H), 7.25 (m, 2H), 7.19 (m, 3H), 4.88 (m, 1H), 4.51 (AB, 2H), 3.88 (s, 3H), 3.79 (AB, 2H), 3.22 (m, 4H), 2.64 (m, 2H), 2.18 (m, 1H), 2.09 (m, 1H). FAB MS, [M+H] = 615. (0.011) (V = 2.11) (0.011) (V = 2.11) (0.011)
- 30 EXAMPLE 161-(5,-2-nibikanycox--9-(lytikanycox--9-(lytikanycox--9-(lytikanycox)-9-(lytikanyc

ch omatopraphy eluting with 60% EtOAc/nexands to afford 7-math/0xv-

EXAMPLE 141, Part Dusing 3-bromomethylthiophene in place of benzyl bromide...The crude product is purified by column chromatography eluting with gradient of 10% Et@Ac/CH2Cl2 to 25% EtQAc/CH2Cl3 to afford the title D-[[1-(2-cyan pyridine-4 ylmathyl)-2-0xccbilogiatidw_8-sa_briugqmoo H NMR (CDCl₃, 300 MHz) δ 8,65 (d, 1H), 8,47 (s₀1H), 7.95 (m, 2H); 7.80 (d, 1H), 7.57 (s, 1H), 7.43 (d, 1H); 7.25 (m, 4H); 7.08 (d, 1H), 4.49 (AB; 2H), 4.45 (m, 3H), 3.94 (s, 3H), 3.19 (m, 2H), 2.34 (m, 1H), 2.20 (m, 1H). gurified by solumn chromatography eluting with gradient of SON EtOACAC 4-{3-(S)-[(7-Methoxynaphthalene-2-sulfonyl)thiophen-3-ylmethylamino]-2-10 oxopyrrolidin-1-ylmethyl)pyridine-2-carboxamidine trifluoroacetate. 7-Methoxynaphthalene-2-sulfonic acid [1-(2-cyanopyridin-4-ylmethyl)-2oxopyrrolidin-3-(S)-yl]thiophen-3-ylmethylamide is converted to the title compound as described in EXAMPLE 154, Part B) The crude product is purified by RP-HPLC eluting in a gradient of 10% CH₃CN/H₂O (0.1% TFA) to 80% CH₃CN/H₂O (0.1% TFA) and the appropriate product fractions are lyophilized to provide the title compound as a white solid any sorten ¹H NMR (DMSO-d₆, 300 MHz) δ 9.43 (bs, 2H), 9.17 (bs, 2H), 8.66 (d, 1H), 8.35 (s, 1H), 7.94 (d, 1H), 7.88 (s, 1H), 7.87, (d, 1H), 7.73, (d, 1H), 7.51 (d) 1H), 7.45 (s, 1H), 7,34 (m, 1H), 7,29 (m, 2H), 6,92 (dil1H), 4,70 (m; 1H), 4:34 (s, 2H), 4.30 (AB, 2H), 3.80 (s, 3H), 3.12 (m, 1H), 3.00 (m, 1H), 2.10 (m, 1H), 1.77 (m, 1H). FAB.MS, [M+H] =550, to reduce a politic CLIP OF ye helbing at 80% CHICN/HIC (0.1% IFA) and the appropriate product fractions an EXAMPLE 162 and be an benogmore ellit edit ebivorg or besilingly 1. A-(3-(S)-[(7-Methoxynaphthalene-2-sulfonyl)thiophen-3-ylmethylaminol-2-25 oxopyrrolidin-1-ylmethyl)thiophene-2-carboxamidine trifluoroacetate. (d. 1H), 7.57 (r. 3H), 7.05 (dd, 1H), 7.25 (m. 2H), 7.19 (m. 3H), 3.83 (b.), 3H), A. 7-Methoxynaphthalene-2-sulfonic acid [1-(2-cyanothiophene-4-ylmethyl)-2oxopyrrolidin-3-(S)-yl]thiophene-3-ylmethylamiden (J-1, m) 90 2 (H) The title compound is prepared from 7-methoxynaphthalene-2-sulfonic acid [1-(2-cyanothiophen-4-ylmethyl)-2-oxopyrrolidin-3-(S)-yl]amide (0.51g, 1.16) mmol) as described in EXAMPLE 126, Part A. using 3-bromomethylthiophene in place of methyl jodide. The crude product is purified by column joxu chromatography eluting with 60% EtOAc/hexanes to afford 7-methoxynaphthalene-2-sulfonic acid-[1-(2-cyanothiophene-4-ylmethyl)-2-oxopyrrolidin-3-(S)-yl]thiophene-3-ylmethylamide.as a white solid (0.18 g, 0.33 mmol).

the die competed is prepared from 7-methoxynapishadour Espliana arbum 12 person wilder 1 yet with 100 exception for 24Shedien ing produce in particular ¹H NMR (CDCl₃, 300 MHz) δ 8.44 (s, 1H), 7.93 (m, 2H), 7.78 (d, 1H), 7.46 (d, 1H), 7.24 (m, 3H), 7.13 (s, 4H), 7.05 (d, 1H), 4.2-4.6 (2AB, 4H), 4.44 (t, 1H), 3.72 (s, 3H), 3.12 (m, 2H), 2.25 (m, 1H), 2.05 (m, 1H). FAB MS, [M+H]*=538.

B. 4-{3-(S)-[(7-Methoxynaphthalene-2-sulfonyl)thiophen-3-ylmethylamino]-2-oxopyrrolidin-1-ylmethyl)thiophene-2-carboxamidine trifluoroacetate.
7-Methoxynaphthalene-2-sulfonic acid [1-(5-cyanothiophen-3-ylmethyl)-2-oxopyrrolidin-3-(S)-yl]thiophene-3-ylmethylamide (0.18, 0.33 mmol) is converted as described in EXAMPLE 125, Part D. The crude product is purified by RP-HPLC eluting in a gradient of 25% CH₃CN/H₂O (0.1% TFA) to 80% CH₃CN/H₂O (0.1% TFA) and the appropriate product fractions are lyophilized to provide the title compound as a white solid (0.083 g, 0.12 mmol).

¹H NMR (DMSO-d_e, 300 MHz) δ 8.43 (s, 1H), 7.92 (d, 1H), 7.83 (m, 4H), 7.39 (s, 1H), 7.28 (m, 2H), 7.17 (s 1H), 6.97 (d, 1H), 4.64 (t 1H), 4.43 (2 AB, 4H), 3.92 (s, 3H), 3.18 (m, 2H); 2.22 (m, 1H), 1.96 (m, 1H). FAB MS, [M+H] ±555.

Elemental analysis calculated with 1 mole of H₂O: C=48.97%, H=4.26%, N=8.16%; found C=48.80%, H=4.34%, N=7.88%.

EXAMPLE 163 *** | The second s

20 4-{3-(S)-[(4-(6-Nîtro-2-chlorophenoxy)benzenesulfonyl)aminoj-2-oxopyrrolidin-1-ylmethyl)thiophene-2-carboxamidine trifluoroacetate. 3 1000 600 2000 0.5 p. 34.1 horogorop alli adi unaty quancy budose

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A. 4-(3-(5)-[(4-(6-Nitro-2-chlorophenoxy)benzenesulfonyl)amino]-2-oxopyrrolidin-1-ylmethyl)thiophene-2-carbononitrile

- 25 4-(3-(S)-[(4-(6-Nitro-2-chlorophenoxy)benzenesulfonyl)amino]-2-oxopyrrolidin-1-ylmethyl)thiophene-2-carbononitrile is prepared as described in EXAMPLE 125, Part C from of 4-(3-Amino-2-oxopyrrolidine-1-ylmethyl)thiophene-2-carbonitrile hydrochloride (0.36 g, 1.4 mmol), and 4-(6-Nitro-2-chlorophenoxy)-benzenesulfonyl chloride (0.63 g, 1.8 mmol) and triethyl amine (0.57 g, 5.7
- and one of the separated; the solution is diluted with CH CI and 0.5 N HCI. The layers are separated; the organic layer is dried over Na.50, filtered and concentrated. The crude product is triturated with ether to afford the title compound (0.72 g, 1.35 mmol) as a white foam.
 - 35 (d, 1H), 7.53 (dd, 1H) 7.02 (d, 2H), 4.42 (AB, 2H), 4.11 (t, 1H), 3.23 (m, 2H), 2.23 (m, 1H), 1.71 (m, 1H). FAB MS, [M+H] =533; 535.

o) 84.7 B. 4-(3-(S)-[(4-(6-Nitro-2-chlorophenoxy)benzenesulfonyl)aminol-2- $23.8 \ (Hi,J) \\ \underline{\text{oxopyrrolidin-1-ylmethyl}} \\ \underline{\text{thiophene-2-carboxamidine: trifluoroacetate}}.$ St 4-(3-(S)-[(4-(6-Nitro-2-chlorophenoxy)benzenesulfonyl)amino]-2-oxopyrrolidin-1-ylmethyl)thiophene-2-carbononitrile (0.408, 0.75 mmol) is converted to the 5 title compound as described in EXAMPLE, 125, Part D; The crude product is purified by repeated RP-HPLC, eluting with a gradient of 10% CH₃CN/H₂O (0.1% TEA) to 100% CH₃CN/H₂O (0.1% TEA). The appropriate product fractions are lyophilized to provide the title compound as a white solid (0.22 g, <u>0,33 mm</u>ol). converted as described in EXAMPLE 125, Part D. H NMR (CD₃OD, 3OO MHz) δ.8.04 (d, 1H), 7.92 (two.d., 3H), 7.86 (s, 1H), 7.78 (s, 1H), 7.56 (dd, 1H) 7.02 (d, 2H), 4.46 (AB, 2H), 4.10 (t, 1H), 3.28 (m, 2H), 2.24 (m, 1H), 1.85 (m, 1H), FAB MS, [M+H] = 550; 552 non elit erit ebivoro ¹H NMP (DMSO- $d_{\rm s}$, 300 MHz) $8.8\,43$ (s, 1H), 7.92 (d, 1H), 7.83 (m, 4H), 7.39 (s, 1H), 7.28 (m, 2H), 7.17 (s 1H), 6.97 (d, 1H), 4.84 (t 1H), 4.6 3) SU.E 15 <u>3-(S)-[(7-Methoxynaphthalene-2-sulfonylamino]-2-oxopyrrolidin-1-ylmethyl}-</u> Figure 151 analysis celculated estate continue trifluoroacetate colculated estate esta N=8.16%; found C=48.20%, H=4.34%, N=7.89%

A. 5-Bromomethylfuran-2-carbononitrile

5-Hydoxymethylfuran-2-carbononitrile (1.12 g, 9.1 mmol), is_dissolved in THF

20 (75 mL), treated with triphenylphosphine (2.9.g, 11.06 mmol), carbon

tetrabromide (3.78 g, 11.4 mmol) and stirred at room temperature for 18 hours.

Standard workup yields the title compound (1.45 g, 7.8 mmol).

1H NMR (CDCl₃, 300 MHz) δ 7.04 (d, 2H), 6.50 (d, 1H), 4.43 (s, 2H).

B. 5-(3-Amino-2-oxopyrrolidine-1-vimethyl)furan-2-carbonitrile hydrochloride

A solution of (2-oxopyrrolidin-3-(S)-yl)carbamic acid tert-butyl ester (1.56 g, 7.8 mmol) in 80 mL of THF:DMF (5:1) is treated with 5-bromomethylfuran-2-carbonitrile (3.23 g, 16 mmol) and sodium hydride (60%) (0.32 g, 8 mmol) as described in EXAMPLE 122. Part F. After addition, the solution is allowed to warm to ambient temperatures. After 5 hours, the solution is quenched by the addition of sat. NH,Cl. The solution is diluted with EtOAc and washed with H₂O (3x) and saturated NaCl. The organic layer is dried over MgSO, filtered and concentrated. The crude product is purified by column chromatography eluting with gradient of 40% EtOAc/hexanes to 80% EtOAc/hexanes to afford [1-(5-cyanofuran-2-ylmethyl)-2-oxopyrrolidin-3-yl]carbamic acid tert-butyl ester (2.38 g, 7.8 mmol) as a white solid. A portion of this material (1.28 g, 4.2 mmol) is

treated as described in EXAMPLE 122, Part G to yield the title compound (1.1 g, 4.55 mmol). 1.1 Carrier St. Co.

¹H NMR (DMSO-d₆, 300 MHz) δ 8.73 (bs, 3H), 7.45 (d, 1H), 6.73 (d, 1H), 4.50 (s, 2H), 3.95 (m, 1H), 3.30 (m, 2H), 2.31 (m, 1H), 1.98 (m, 1H). EI MS, M=205.

C. 7-Methoxynaphthalene-2-sulfonic acid [1-(2-cyanofuran-5-vlmethyl)-2oxopyrrolidin-3-(S)-yl]- amide.

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7-Methoxynaphthalene-2-sulfonic acid [1-(2-cyanofuran-5-ylmethyl)-2oxopyrrolidin-3-(S)-yl]amide is prepared as described in EXAMPLE 125. Part C

- 10 from of 5-(3-amino-2-oxopyrrolidine-1-ylmethyl)furan-2-carbonitrile hydrochloride (1.1 g, 4.55 mmol), and 7-methoxynaphthalene-2-sulfonyl chloride (1.52 g, 5.9 mmol). After 16 hours, the solution is diluted with CH₂Cl₂. The organic layer is washed with 0.5 N HCl, water and sat. NaCl. The organic layer is dried over Na SO, filtered and concentrated. The crude product is
- purified by column chromatography eluting with 10% EtOAc/CH,Cl, to afford 15 the title compound (0.88 g, 2.07 mmol) as a white solid. H NMR (CDCl₃, 300 MHz) δ 8.33 (s, 1H), 7.86 (d, 1H), 7.74 (m, 2H), 7.27 (dd, 1H), 7.22 (d, 1H), 6.97 (d, 1H), 6.35 (d, 1H), 5.61 (d, 1H), 4.40 (AB, 2H), 3.93 (s. ~ 3H), 3.73 (m, 1H), 3.28 (m, 2H), 2.57 (m, 1H), 2.08 (m, 1H). EI MS, [M]+=425. - **20**go Cog Back Program (Program of the transfer for stable of **さり**) (関す

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- D. 5-{3-(S)-[(7-Methoxynaphthalene-2-sulfonylamino]-2-oxopyrrolidin-1-<u>vlmethvllfuran-2-carboxamidine trifluoroacetate.</u>
- 7-Methoxynaphthalene-2-sulfonic acid-[1-(2-cyanofuran-5-vimethyl)-2oxopyrrolidin-3-(S)-yl]amide (0.355/g) 0.83 mmol) is converted as described in
- 25 EXAMPLE 125; Part D. The crude product is purified by RP-HPLC eluting in a gradient of 10% CH2CN/H2O (0.1% TFA) to 100% CH2CN and the appropriate product fractions are dyophilized to provide the title compound as a white solid washing (0.365ig, 0.625 mmol) work back ut 8 - kerutanegmet melidina in allaw
 - 300 MHz) δ 8.40 (s; 1H), 7.94 (d; 1H), 7.87 (d, 1H), 7.74 30 si(dd, 1H); 7.48 (d, 1H); 7.38 (d, 1H); 7.28 (dd, 1H); 6.64 (d; 1H); 4.53 (AB, 2H), 4:14 (t, 1H), 3.93 (s, 3H), 3.28 (m, 2H), 2:12 (m, 1H), 1:74 (m, 1H). FAB MS. [M+H] =443. Elemental analysis calculated with 1.5 mole of H₂O: C=47.34%. H=4.49% N=9.61%; found C=47.25%, H=4.05%, N=9.13%; H=4.05%

114, 3.35 (m. 2H) 2.43 (m. H), 1.80 (m. H)

3 C

35 **EXAMPLE 165**

4-(3-(S)-(5-Chloro-3-methylbenzolb)thiophene-2-sulfonylamino)-2oxopyrrolidin-1-vlmethyl)furan-2-carboxamidine trifluoroacetale

project. 4.4-Hydroxymethylfuran-2-carbonitrile AXE nebodhozele de Dassen A solution of furan-3-ylmethanol (9.68 g; 98.7 mmol) in THF (150 mL) at -78°C is treated with n-butyl lithium (65 mL/of-1.6 M/solution) for 1 hour followed by and s-butyl lithium (86 mL of 1.3 M solution) for 4-hours. CA solution of lodine (29 g, 114 mmol) in THF (250 mL) is added and the solution is slowly warmed Sarry to room temperatures: After stirring overnight the reaction mixture is diluted with ether, washed with brine, dried (MgSO4) and concentrated. Chromatographic s purification (30% ethyl acetate/hexane) yielded the title compound as a dark red oil (13-7 g, 61.2 mmol) contaminated with furan-3-ŷlmethanol. This material is treated as described in EXAMPLE 122, Part C; the crude product is chromatographed with ethyl acetate/hexane (30-40%) to yield pure title oniorica (1.25 g, 5.9 mmol). After to allowing \$3.6 (1.25 g, 10.1) mmol). 1H NMR (CDCl₃, 300 MHz) δ 7.53 (s, 1H), 7.14 (s, 1H), 4.56 (s, 2H); EI MS. layer is dised over Ne, SO, filtered and concentrated. The crest Wayor is purified by column chip natography engling with 10% EtQAc/CH₂CL to 3.21 ... B. 3-Bromomethylfuran-5-carbonitrile 0.8 (a 84 b) time emporabilities The title compound is prepared as described in EXAMPLE 122, Part D except that:4-hydroxymethylthiophene-2-carbonitrile is replaced with 4-hydroxymethyl-furan-2-carbonitrile (1.24 g. 10.1 mmol); yield: (0.78 g. 3.9 mmol). 20 ¹H NMR (CDCl₃, 300 MHz) δ 7.59 (s, 1H), 7.12 (s, 1H), 4.30 (s, 2H); EI MS, M⁺ =

C: 4-(3-Amino-2-oxopyrrolidine-1-ylmethyl)furan-2-carbonitrile tent-1

A solution of (2-oxopyrrolidine-3-(S)-yl)carbamic acid tent-butyl ester (0.78 g, 3.9 mmol) in 40 mL of THF:DMF (5:1) is treated with 3-bromomethylfuran-5- decarbonitrile (0.73 g, 3.9 mmol) and sodium hydride (60%) (0.10 g, 4.2 mmol) as described in EXAMPLE 122, Part F. After addition; the solution is allowed to warm to ambient temperatures. Standard workup followed by chromatography (5-10% MeOH/CH₂Cl₂) affords [1-(2-cyanofuran-4-ylmethyl)-2-oxopyrrolidin-3-30 (yl]carbamic acid tent-butyl ester (1:05 g, 7.8 mmol) as a white solid. This omaterial is treated with trimethylsilyliodide (0.844 g, 4.22 mmol) and free based with Amberlite (OH) resin to yield the title compound (0.926 g, 4.51 mmol). 1H NMR (CD₃OD, 300 MHz) § 7,80 (s, 1H); 7.28 (s, 1H); 4.36 (AB, 2H); 3.72 (t, 1H), 3.38 (m, 2H), 2.43 (m, 1H), 1.80 (m, 1H).

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D. 5-Chloro-3-methylbenzo[b]thiophene -2-sulfonic acid [1-(2-cyano-furan-4-ylmethyl)-2-oxopyrrolidin-3-(S)-yllamide.

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The title compound (0.25 g, 0.56 mmol) is prepared as in EXAMPLE 125, Part C, using 5-chloro-3-methylbenzo[b]thiophene-2-sulfonyl chloride (0.39 g, 1.39 mmol) and 3-(3-amino-2-oxopyrrolidin-1-ylmethyl)furan-2-carbononitrile (0.25 g, 1.22 mmol).

¹H NMR (CDCl₃, 300 MHz) δ 7.78 (s, 1H), 7.73 (d, 1H), 7.49 (s, 3H), 7.45 (d, 1H), 5.78 (bs, 1H), 4.28 (s, 2H), 3.87(m, 1H), 3.23 (m, 2H), 2.66 (s, 3H), 2.55 (m, 1H), 2.05 (m, 1H).

E. 4-[3-(S)-(5-Chloro-3-methylbenzolb)thiophene-2-sulfonylamino)-2-10 oxopyrrolidin-1-vlmethyl]furan-2-carboxamidine trifluoroacetate. 5-Chloro-3-methylbenzo[b]thiophene-2-sulfonic acid [1-(2-cyáno-furan-4ylmethyl)-2-oxopyrrolidin-3-(S)-yl]amide (0.24 g, 0.53 mmol) is converted to the title compound as described in EXAMPLE 125, Part D. The crude product is purified by RP-HPLC eluting in a gradient of 20% CH₃CN/H₂O (0.1% TFA) to 80% CH₂CN/H₂O (0.1% TFA) and the appropriate product fractions are 15 lyophilized to provide the title compound as a white solid (0.12 g, 0.2 mmol). ¹H NMR (DMSO-d_s, 300 MHz) δ 9.21 (bs, 2H), 9.10 (bs, 2H) 8.68 (d, 1H), 8.09 (m, 3H), 7.54 (m 2H), 4.19 (AB, 2H), 4.14 (m, 1H), 3.15 (m, 2H), 2.60 (s. 3H). 2.02 (m, 1H), 1.63 (m, 1H). FAB MS, [M+H]+=467. Elemental analysis 20 calculated with 1.5 mole of H₂O: C=41.48%, H=3.81%, N=9.21%; found C=41.51%, H=3.41%, N=8.84%.

Other compounds prepared according to the procedures above include those encompassed by the following formula:

wherein R is hydrogen, methyl, aralkyl, heteroaralkyl, HO_2CCH_2 -, $HOC(O)CH_2$ -, $H_2NC(O)CH_2$ -, (aralkyl) $HNC(O)CH_2$ - or (heteroaralkyl) $HNC(O)CH_2$ -; X_6 is hydrogen or amino; and R_1 is selected from the group of formulae

The File configuration 25 groups to 65 mmultiple orapores that in the MM \$10.125 Factor C. being 5-citizro-3-match controlled in presultarial for sultarial for an action of the citizens of the sultarial for action of the citizens of the sultarial for action of the citizens of t O NME (CDC), 300 NEL) 8 1.72 (3, 1H), 1.43 (3, 1H) 7.49 (8, 3H), 1.45 (3 PLUNE MER MER OF SECTION STATE OF PRINTERS OF SECTION OF THE SECTI , h, HOS (HG, 🏗) ƏÇSQ (H ELALES HOLD on a size Dybe at 20th a strate 2-surfacely 19 12 1-61 Personalist Capping Section Service (1974) Company of the property of the contract of at the second of FEXAMPLE 175, Pacific The curde produg is nurffied on RP-HPLC souting to a gradient of 20% C.F., NVH₂O (O 9% TFA) of ยนให้ ChijON/HijO (ป.ก.บ. 1.ก.บ. and give appropricia product เป็นผู้สัญษา कर्मुंखी सुंख संस्थितिक के प्रमाण के के प्रमाण के किया है। कि के किया के किया के किया के किया के किया के किया क 1. (bs. 141), B.CH (का. टी.) 7.54 (ता 2म) १ -९ (स.६. 2म) 4.1 - एक मन् 3.15 १० वर्ग, 2.10 के वर्ग J. CL. T. Hay, THE HOWER SAMES WASHINGED, Eleman Williams Washing Cinal <u>com</u>oveds prepared accordings. It is uron 10

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Other compounds prepared according to the procedures above include those encompassed by the following formula:

wherein R is hydrogen, methyl, aralkyl, heteroaralkyl, HO₂CCH₂-, HOC(O)CH₂-, H₂NC(O)CH₂-, (aralkyl)HNC(O)CH₂- or (heteroaralkyl)HNC(O)CH₂-; and R₁ is selected from the group of formulae

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The molecules described herein inhibit blood coagulation by virtue of their ability to inhibit the penultimate enzyme-in the coagulation cascade, controlling the activity of Factor Xa. Both the activity of free Factor Xa and Factor Xa assembled in the prothrombinase complex (Factor Xa, Factor Va, calcium and phospholipid) are inhibited by compounds of formula 1. The inhibition of the Factor Xa activity is obtained by direct complex formation between the inhibitor and the enzyme and is therefore independent of the plasma co-factor antithrombin III. Effective inhibition of the Factor Xa activity is achieved by administering the compounds either by oral administration, continuous intravenous infusion, bolus intravenous administration or any other parenteral route such that it achieves the desired effect of preventing the activity of Factor Xa induced formation of thrombin from prothrombin.

Anticoagulant therapy is indicated for the treatment and prophylaxis of a so variety of thrombotic conditions of both the venous and arterial vasculature. In the arterial system, abnormal thrombus formation is primarily associated with arteries of the coronary, cerebral and peripheral vasculature. The diseases associated with thrombotic occlusion of these vessels principally include acute myocardial infarction (AMI), unstable angina, thromboembolism, acute vessel closure associated with thrombolytic therapy and percutaneous transluminal coronary angioplasty (PTCA), transient ischemic attacks, stroke intermittent claudication and bypass grafting of the coronary (CABG) or peripheral arteries. Chronic anticoagulant therapy may also be beneficial in preventing the vessel 25 luminal narrowing (restenosis) that often occurs following PTCA and CABG. and in the maintenance of vascular access patency in long-term hemodialysis patients. With respect to the venous vasculature, pathologic thrombus formation frequently occurs in the veins of the lower extremities following abdominal, knee and hip surgery (deep vein thrombosis, DVT). DVT further predisposes the patient to a higher risk of pulmonary thromboembolism. A systemic, disseminated intravascular coagulopathy (DIC) commonly occurs in both vascular systems during septic shock, certain viral infections and cancer. This condition is characterized by a rapid consumption of coagulation factors 35 and their plasma inhibitors resulting in the formation of life-threatening

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thrombin throughout the microvasculature of several organ systems. The indications discussed above include some, but not all, of the possible clinical situations where anticoagulant therapy is warranted. Those experienced in this field are well aware of the circumstances requiring either acute or chronic prophylactic anticoagulant therapy.

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These compounds may be used alone or in combination with other diagnostic, anticoagulant, antiplatelet or fibrinolytic agents. For example adjunctive administration of inhibitors of the activity of Factor Xa with standard heparin, low molecular weight heparin, direct thrombin inhibitors (i.e. hirudin), aspirin, fibrinogen receptor antagonists, streptokinase, urokinase and/or tissue plasminogen activator may result in greater antithrombotic or thrombolytic efficacy or efficiency. The compounds described herein may be administered to treat thrombotic complications in a variety of animals such as primates including humans, sheep, horses, cattle, pigs, dogs, rats and mice. Inhibition of factor Xa is useful not only in the anticoagulant therapy of individuals having thrombotic conditions but is useful whenever inhibition of blood coagulation is required such as to prevent coagulation of stored whole blood and to prevent coagulation in other biological samples for testing or storage. Thus, any 20 inhibitor of Factor Xa activity can be added to or contacted with any medium containing or suspected of containing Factor Xa and in which it is desired that ം _ blood coagulation be inhibited. െ വു നാ വേദ്യാല് കേ a will a verticus narat, ii i organio solicans. Tui cium peditions may c

and the responsibilities and the second seco 25 activity may find utility in the treatment or prevention of other physiological conditions in which the generation of thrombin has been implicated as playing a pathologic role: For example, thrombin has been proposed to contribute to the morbidity and mortality of such chronic and degenerative diseases as arthritis, cancer, atherosclerosis and Alzheimer's disease by virtue of its ability 30 to regulate many different cell types through specific cleavage and activation of a cell surface thrombin receptor. Inhibition of factor Xa activity will effectively block thrombin generation and therefore neutralize any pathologic effects of at thrombinition various cell types command of between all or a clisivond

35 According to a further feature of the invention there is provided a method for the treatment of a human or animal patient suffering from, or subject to, a physiological condition which can be ameliorated by the administration of an

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and inhibitor of the Factor Xa activity, for example conditions as hereinbefore sounding elidescribed, which comprises the administration to the patient of albre स्तर Leantherapeutically effective amount of compound of formula I or a composition ுற்ற gontaining a compound of formula lau"Effective amount" is meant to describe an amount of compound of the present invention effective in inhibiting the activity of Factor Xa and thus producing the desired therapeutic effect.

These compounds may as alsone or in commitmental with ether nighters a The present, invention also includes within its scope pharmaceutical bechairs formulations which comprise at least one of the compounds of formula I in _____10,___association with a pharmaceutically acceptable carrier or coating. aspiral, fibrinogen receptor antagonists, cheptokinase, utoʻtinase attaʻor titaslphaand the properties of the present invention may generally be ை நடிக்குள்ளுக்குறு parenterally, sintravenously, subcutaneously intramuscularly, oscolonically anasally, intraperitoneally a rectally or orally as a moral tasm including hitnans, sheep, horses, cattle, pigs, dogs, tals and nice. Inhidton erfical alaubiviThe products according to the invention may be presented in forms and the invention also mey are grelates to pharmaceutical compositions containing at least one product according to the invention which are suitable for use in human or veterinary 720 medicine. These compositions may be prepared according to the customary ed book methods, using one or more pharmaceutically acceptable adjuvants or excipients. The adjuvants comprise, interalia, diluents esterile aqueous media and the various non-toxic organic solvents. The compositions may be A value presented in the form of tablets, pills, granules, powders, aqueous solutions or 25 suspensions, injectable solutions, elixirs or syrups, and can contain one or served agents chosen from the group comprising sweeteners, flavorings, colorings, or stabilizers in order to obtain pharmaceutically acceptable preparations, and the property of such of roll call sense was from ent

arthilist if ancer, atherovoletoels and Alzhainter's disease by thus or its highly 30 to a bine The choice of vehicle and the content of active substance in the vehicle are generally determined in accordance with the solubility and chemical properties of the product, the particular mode of administration and the provisions to be observed in pharmaceutical practice. For example, excipients such as lactose, sodium citrate, calcium carbonate, dicalcium phosphate and 35 disintegrating agents such as starch; alginic, acids and certain complex 35 or sillicates combined with lubricants such as magnesium stearate, sodium lauryl sulfate and talc may be used for preparing tablets. To prepare a capsule, it is

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advantageous to use lactose and high molecular weight polyethylene glycols. When aqueous suspensions are used they can contain emulsifying agents or agents which facilitate suspension. Diluents such as sucrose, ethanol, polyethylene glycol, propylene glycol, glycerol and chloroform or mixtures thereof may also be used. From the last disposition of Suppliers

For parenteral administration, emulsions, suspensions or solutions of the products according to the invention in vegetable oil, for example sesame oil, groundnut oil or olive oil, or aqueous-organic solutions such as water and propylene glycol, injectable organic esters such as ethyl oleate, as well as sterile aqueous solutions of the pharmaceutically acceptable salts, are used. The solutions of the salts of the products according to the invention are especially useful for administration by intramuscular or subcutaneous injection. The aqueous solutions, also comprising solutions of the salts in pure distilled water, may be used for intravenous administration with the proviso that their pH is suitably adjusted, that they are judiciously buffered and rendered isotonic with a sufficient quantity of glucose or sodium chloride and that they are sterilized by heating, irradiation or microfiltration. Control to the control of the contro

20⁶0 3 Suitable compositions containing the compounds of the invention may be prepared by conventional means. For example, compounds of the invention may be dissolved or suspended in a suitable carrier for use in a nebulizer or a suspension or solution aerosol, or may be absorbed or adsorbed onto a suitable solid carrier for use in a dry powder inhaler. Factor Xa in highlight Enzymie Assert Miemods 25

Solid compositions for rectal administration include suppositories formulated in accordance with known methods and containing at least one ncompound of formula I. was entructed to accept the third the entruction

The percentage of active ingredient in the compositions of the invention may be varied, it being necessary that it should constitute a proportion such that a suitable dosage shall be obtained. Obviously, several unit dosage forms may be administered at about the same time. The dose employed will be determined by the physician, and depends upon the desired therapeutic effect, 35 the route of administration and the duration of the treatment, and the condition of the patient. In the adult, the doses are generally from about 0.01 to about 100, preferably about 0.01 to about 10, mg/kg body weight per day by

inhalation, from about 0.01 to about 100, preferably 0.1:to 70, more especially 0.5 to 10, mg/kg body weight per day by oral administration, and from about 0.01 to about 50, preferably 0.01 to 10, mg/kg body weight per day by intravenous administration. In each particular case, the doses will be determined in accordance with the factors distinctive to the subject to be a treated, such as age, weight, general state of health and other characteristics which can influence the efficacy of the medicinal product.

The products according to the invention may be administered as frequently as necessary in order to obtain the desired therapeutic effect. Some patients may respond rapidly to a higher or lower dose and may find much weaker maintenance doses adequate. For other patients, it may be necessary to have long-term treatments at the rate of 1 to 4 doses per day, in accordance with the physiological requirements of each particular patient. Generally, the active product may be administered orally 1 to 4 times per day; It goes without saying that, for other patients, it will be necessary to prescribe not more than one or two doses per day, bos to product the patients of the physiological requirements of the physiological requirements of each particular patient.

Compounds within the scope of the present invention exhibit marked
pharmacological activities according to tests described in the literature which
tests results are believed to correlate to pharmacological activity in humans
and other mammals. The following pharmacological test results are typical
characteristics of compounds of the present invention as to control of

startized by healing, irradiation or misroliticall as

เรียกใช้ เลี้ยงการ รูด้ ละกับ เกษ าดโบค์เทยก อันโดย คำว่ามีเมื่อ อังกิด อัคการ เห 25 Factor Xa Inhibitor: Enzyme Assay Methods

Please find below a section describing the methods used for evaluating the activity of the compounds used in the factor Xa program for insertion into the patent.

ราษสมาก ลาง มีเลยูตามงาอส์ ค่า Inelt signi มาปัติมาติ จดุลที่สะคอด อดีไ **Enzyme Assays:** เวลเซอก (สายใหญ่ เลย เมื่อสมาชาย hands มีวัตส์ ราชสมาชายสมาชาย (สายมาติ ราชยามาติ รุปภา

The ability of the compounds in the present invention to act as inhibitors of factor Xa, thrombin, trypsin, tissue-plasminogen activator (t-PA), urokinase-plasminogen activator (u-PA), plasmin and activated protein C is evaluated by determining the concentration of inhibitor which resulted in a 50% loss in enzyme activity (IC50) using purified enzymes.

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All enzyme assays are carried out at room temperature in 96-well microtiter plates using a final enzyme concentration of 1 nM. The concentrations of factor Xa and thrombin are determined by active site titration 5 and the concentrations of all other enzymes are based on the protein concentration supplied by the manufacturer. Compounds according to the invention are dissolved in DMSO, diluted with their respective buffers and assayed at a maximal final DMSO concentration of 1.25%. Compound dilutions are added to wells containing buffer and enzyme and pre-equilibrated 10 for between 5 and 30 minutes. The enzyme reactions are initiated by the addition of substrate and the color developed from the hydrolysis of the peptide-p-nitroanilide substrates is monitored continuously for 5 minutes at 405 nm on a Vmax microplate reader (Molecular Devices). Under these conditions. less than 10% of the substrate is utilized in all assays. The initial velocities 15 measured are used to calculate the amount of inhibitor which resulted in a 50% reduction of the control velocity (IC50). The apparent Ki values are then determined according to the Cheng-Prusoff equation (IC50 = Ki [1+[S]/Km]) assuming competitive inhibition kinetics.

20 By way of example, 5-pyrid-2-yl-thiophene-2-sulfonic acid {1-[3-aminoiminomethyl)benzyl]-2-oxopyrrolidin-3-(S)-yl}amide trifluoroacetate has a Ki value of 100 nM.

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m பாகளையா**By way of example, 7-methoxy naphthalene-2-sulfonic acid (1-[3-25ா (aminoiminomethyl)benzyl]-2-oxopyrrolldinf3=(S)-yl)acid trifluoroacetate has a be ki value of 35 nM. சிர் இவி விக்கையில் மிக்கை நாய்கள் ஆய்க் இது கூர்கள் கொண்கி வரிக்கா நி. இது நி. இதி விக்கி நாக்கி விக்கி காகி**

An additional in vitro assay may be used to evaluate the potency of compounds according to the invention in normal human plasma. The activated 30 partial thromboplastin time is a plasma-based clotting assay that relies on the in situ generation of factor Xa, its assembly into the prothrombinase complex and the subsequent generation of thrombin and fibrin which ultimately yields the formation of a clot as the assay endpoint. This assay is currently used clinically to monitor the ex vivo effects of the commonly used anticoagulant drug heparin as well as direct acting antithrombin agents undergoing clinical evaluation. Therefore, activity in this in vitro assay is considered as a surrogate marker for in vivo anticoagulant activity.

Human Plasma Based Clotting Assay: The EVECUR & TYRING ILA Activated partial thromboplastin clotting times are determined in duplicate on a MLA Electra 800 instrument. A volume of 100 μl of citrated normal human pooled plasma (George King Biomedical) is added to a cuvette containing 100 ul of a compound according to the invention in Tris/NaCl buffer (pH 7.5) and placed in the instrument. Following a 3 minute warming period the instrument automatically adds 100 µl of activated cephaloplastin reagent (Actin, Dade) followed by 100 µl of 0.035 M CaCl2 to initiate the clotting reaction. Clot dripped for services and provided the control of th Compound potency is quantitated as the concentration required to double a control clotting time measured with human plasma in the absence of the encetting compound according to the invention case reactions and according to the invention case reactions are the conditions. less than 10% of the substrate is utilized in all essays. The initial velocities 15 to be like A compound according to the invention may also be evaluated for their ran in vivo antithrombotic efficacy in two well established animal experimental models of acute vascular thrombosis. A rabbit model of jugular vein thrombosis and a rat model of carotid artery thrombosis are used to demonstrate the antithrombotic activity of these compounds in distinct animal model paradigms of human venous thrombosis and arterial thrombosis, oc respectively, each control of the second of

Experimental In Vivo Rabbit Venous Thrombosis Model:

This is a well characterized model of fibrin rich venous thrombosis that is validated in the literature and shown to be sensitive to several anticoagulant drugs including heparin (Antithrombotic Effect of Recombinant Truncated Tissue Factor Pathway Inhibitor (TFPI 1-161) in Experimental Venous Thrombosis a Comparison with Low Molecular Weight Heparin, J. Holst, B. Lindblad, D. Bergqvist, O. Nordfang, P.B. Ostergaard, J.G.L. Retersen, G. Nielsen, and U. Hedner. Thrombosis and Haemostasis. 71, 214-219 (1994).

The purpose of utilizing this model is to evaluate the ability of compounds to prevent the formation of venous thrombi (clots) in vivo generated at a site of injury and partial stasis in the jugular veing the stoles to nothermole.

Male and female New Zealand white rabbits weighing 1.5-2 kg are an anesthetized with 35 mg/kg of ketamine and 5 mg/kg xylazine in a volume of

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a 'Gilvalue of 100 nh.

1 mVkg (i.m.). The right jugular vein is cannulated for infusion of anesthetic (ketamine/xylazine 17/2.5 mg/kg/hr at a rate of approximately 0.5 ml/hr) and administration of test substances. The right carotid artery is cannulated for recording arterial blood pressure and collecting blood samples. Body 5 15 temperature is maintained at 39°C with a GAYMAR T-PUMP. The left external jugular vein is isolated and all side branches along an exposed 2-3 cm of vessel are tied off. The internal jugular vein is cannulated, just above the bifurcation of the common jugular, and the tip of the cannula is advanced just proximal to the common jugular vein. A 1 cm segment of the vein is isolated 10 with non-traumatic vascular clamps and a relative stenosis is formed by tying a ligature around the vein with an 18G needle just below the distal most clamp. This creates a region of reduced flow and partial stasis at the injury site. The isolated segment is gently rinsed with saline 2-3 times via the cannula in the internal jugular. Thereafter the isolated segment is filled with 0.5 ml of 0.5% polyoxyethylene ether (W-1) for 5 minutes. W-1 is a detergent which disrupts the endothelial cell lining of the segment, thus providing a thrombogenic surface for initiating clot formation. After 5 minutes the W-1 is withdrawn from the segment, and the segment is again gently rinsed with saline 2-3 times. The wascular clamps are then removed, restoring blood flow through this portion of 20 the vessel. Clot formation is allowed to form and grow for 30 minutes after which the vein is cut just below the stenotic ligature and inspected for blood flow (the absence of blood flow is recorded as complete occlusion). The entire isolated segment of Vein is then ligated and the formed clot is removed and weighed (wet weight). The effect of test agents on final clot weights is used as 25" the primary end point. Animals are maintained for an additional thirty minutes To a ofter obtain a final pharmacodynamic measure of anticoagulation. Drug administration is initiated 15 minutes prior to vascular injury with W-1 and Continued through the period of clot formation and maturation. Three blood samples (3 mt ea.) are obtained for evaluation of hemostatic parameters: one 30 just prior to administration of W-1; a second 30 minutes after removal of the vascular clamps and a third at the termination of the experiment. Antithrombotic efficacy is expressed as a reduction in the final clot weight in preparations treated with a compound according to the invention relative to The hold rear rate are monitored an act behaviors are are made but woll but a serious and but and but a serious and but a serious and but a serious and a se morares infolloung occlusion of the vessel (defined as the et nimment of 266)

Experimental In Vivo Rat Arterial Thrombosis Model:

Pitachaene to no he antithrombotic efficacy of factor Xa inhibitors against platelet-rich arterial thrombosis may be evaluated using a well characterized rat carotid artery FeCl2-induced thrombosis model (Superior Activity of a Thromboxane Receptor Antagonist as Compared with Aspirin in Rat Models of Arterial and Venous Thrombosis, W.A. Schumacher, C.L. Heran, J.E. Steinbacher, S. Youssef and M.L. Ogletree. Journal of Cardiovascular Pharmacology, 22, 526-533 (1993); Rat Model of Arterial Thrombosis Induced by Ferric Chloride, K.D. Kurtz, B.W. Main, and G.E. Sandusky. Thrombosis Research, 60, 269-280 (1990); The Effect of Thrombin Inhibition in a Rat Arterial Thrombosis Model, 10 R.J. Broersma, L.W. Kutcher and E.F. Heminger. Thrombosis Research 64, 405-412 (1991). This model is widely used to evaluate the antithrombotic lört alamp. potential of a variety of agents including heparin and the direct acting thrombin isolated segment is gently rinsed with saline 2-3 times via the cannula tuernal juguler. The eafter the isolated segment is littled with 0.5 ml of Q. De 15 Sprague Dawley rats weighing 375-450 g-are anesthetized with sodium pentobarbital (50 mg/kg i.p.). Upon reaching an acceptable level of anesthesia, the ventral surface of the neck is shaved and prepared for aseptic surgery. Electrocardiogram electrodes are connected and lead II is monitored throughout the experiment. The right femoral vein and artery are cannulated with PE-50 tubing for administration of a compound according to the invention and for obtaining blood samples and monitoring blood pressure, respectively. A midline incision is made in the ventral surface of the neck. The trachea is exposed and intubated with PE-240 tubing to ensure airway patency. The right carotid artery is isolated and two 4:0 silk sutures are placed around the vessel **25** estunin to facilitate instrumentation. An electromagnetic flow probe (0.95-1.0 mm lumen) is placed around the vessel to measure blood flow. Distal to the probe a 4x4 mm strip of parafilm is placed under the vessel to isolate it from the surrounding muscle bed. After baseline flow measurements are made, a 2x5 troof 3 mm strip of filter paper previously saturated in 35% FeCl2 is placed on top of the vessel downstream from the probe for ten minutes and then removed. The FeCl₂ is thought to diffuse into the underlying segment of artery and cause deendothelialization resulting in acute thrombus formation. Following application of the FeCl2-soaked filter paper, blood pressure, carotid artery blood flow and heart rate are monitored for an observation period of 60 35 minutes. Following occlusion of the vessel (defined as the attainment of zero blood flow), or 60 minutes after filter paper application if patency is maintained,

the artery is ligated proximal and distal to the area of injury and the vessel is

excised. The thrombus is removed and weighed immediately and recorded as the primary end point of the study.

Following surgical instrumentation a control blood sample (B1) is drawn. 5 All blood samples are collected from the arterial catheter and mixed with sodium citrate to prevent clotting. After each blood sample, the catheter is flushed with 0.5 ml of 0.9% saline. A compound according to the invention is administered intravenously (i.v.) starting 5 minutes prior to FeClo application. The time between FeCl₂ application and the time at which carotid blood flow reached zero is recorded as time to occlusion (TTO). For vessels that did not 10 occlude within 60 minutes, TTO is assigned a value of 60 minutes. Five minutes after application of FeCl2, a second blood sample is drawn (B2). After 10 minutes of FeCl₂ exposure, the filter paper is removed from the vessel and the animal is monitored for the remainder of the experiment. Upon reaching zero blood flow blood a third blood sample is drawn (B3) and the clot is 15 removed and weighed. Template bleeding time measurements are performed on the forelimb toe pads at the same time that blood samples are obtained. Coagulation profiles consisting of activated partial thromboplastin time (APTT) and prothrombin time (PT) are performed on all blood samples. In some 20 instances a compound according to the invention may be administered orally. Rats are restrained manually using standard techniques and compounds are administered by intragastric gavage using a 18 gauge curved dosing needle (volume of 5 ml/kg). Fifteen minutes after intragastric dosing, the animal is anesthetized and instrumented as described previously. Experiments are then 25 performed according to the protocol described above alencing

The present invention may be embodied in other specific forms without departing from the spirit or essential attributes thereof and before some

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By is obtionably out adduced aught opportably substituted applicately to aphinistly substituted a substitute of area of area of a characteristic and a consonally substituted materiarially for By and British args her whome and additionally substituted at a consonal and a country of a consonal area of a consonal area.

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1. A compound of formula I

Polloving surgreet instrumentation a nultroliblood sample (81) (13) through All blood samples are collected this sarteful ontheter and mixed with reach blood saliting the day later is of notherest entrophic cost havegag 7.0 to im 8.0 rfflw Ledsini verief carotid binned active the time cotween FeCty application and the time a Sociusion (TTV). For vessels en administration l assigned a value of 60 minutes. Five noit NHR2s some sommin As second blood sangle in crawn (D2). After 10 character of FeOig enticate, the filter paper is removed ficial the vincer and the animal is monitored for the renalisder of the experiment. zeru bland frow blood lpha third blood same's is drawn (E3) and $\ln \ln A$ troine common de la principal de la completa de la principal de la proposición de la proposición de la principal de la princip A is hydrogen, optionally substituted alkyl, optionally substituted aralkyl, 10 optionally substituted heteroaralkyl or hydroxyalkyl; ern abi**R, is hydrogen, R, s(O),- or R, R, Ns(O),-:** the mem hadinated the stable were or philed beyond **equep** to a galent egelsprinterpetic yet be established. He high and police of secretaring setting the setting of the setti 15 hydrogen, optionally substituted lower alkyl, optionally substituted aralkyl or optionally substituted heteroaralkyl;

R₃ Is optionally substituted alkyl, optionally substituted cycloalkyl, optionally substituted aryl, optionally substituted aryl, optionally substituted heteroaryl, optionally substituted aralkyl, optionally substituted heteroaralkyl, optionally substituted aralkenyl or optionally substituted heteroaralkenyl, or R and R₃ taken together form a 5 to 7 membered ring; and

 R_4 is optionally substituted alkyl, optionally substituted cycloalkyl or optionally substituted aryl, optionally substituted heteroaryl, optionally substituted aralkyl or optionally substituted heteroaralkyl, or R_3 and R_4 taken together with the nitrogen to which R_3 and R_4 are attached form an optionally substituted 4 to 7 membered heterocyclyl;

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 X_1 and X_2 are independently selected from hydrogen, optionally substituted alkyl, optionally substituted aryl, optionally substituted aralkyl, optionally substituted heteroaryl, optionally substituted heteroarylkyl or hydroxyalkyl, or X_1 and X_2 taken together form oxo;

 X_2 and X_2 are hydrogen, or taken together form oxo;

X₃ is hydrogen, hydroxy, optionally substituted alkyl, optionally substituted aryl, optionally substituted heteroaryl, optionally substituted aralkyl or optionally substituted heteroaralkyl, or X₃ and one of X₄ and X₅, taken together form a 4 to 7 membered ring;

 X_5 and X_6 , are hydrogen or taken together are =NR₅; complete 9.03×10^{-3} complete

 R_s is hydrogen, $R_sO_2C_7$, R_sO_7 , cyano, R_sCO_7 , optionally substituted lower alkyl, nitro or $Y^1Y^2N_7$; Y^2N_7

Y' and Y' are independently hydrogen, alkyl, aralkyl or heteroaralkyl;

 X_6 and X_6 are independently hydrogen, $R_7R_8N_7$, R_9O_7 , $R_7R_8N_7$, R_9O_7 , R_9C_7 , halo, cyano or nitro;

A Rais hŷdrogen, optionally substituted lower alkyl or optionally substituted aralkyl or optionally substituted heteroaralkyl;

30 R₇ and R₈ are independently hydrogen or optionally substituted lower alkyl, or one of R₇ and R₈ is hydrogen and the other of R₇ and R₈ is R₁₀(O)CCH₂- or lower acyl; and in the other of R₇ and R₈ is R₁₀(O)CCH₂- or lower acyl; and it is the other of R₇ and R₈ is R₁₀(O)CCH₂- or lower acyl; and it is the other of R₇ and R₈ is R₁₀(O)CCH₂- or lower acyl; and it is the other of R₇ and R₈ is R₁₀(O)CCH₂- or lower acyl; and it is the other of R₇ and R₈ is R₁₀(O)CCH₂- or lower acylination of the other of R₇ and R₈ is R₁₀(O)CCH₂- or lower acylination of the other of R₇ and R₈ is R₁₀(O)CCH₂- or lower acylination of the other of R₇ and R₈ is R₁₀(O)CCH₂- or lower acylination of the other of R₇ and R₈ is R₁₀(O)CCH₂- or lower acylination of the other of R₇ and R₈ is R₁₀(O)CCH₂- or lower acylination of the other of R₇ and R₈ is R₁₀(O)CCH₂- or lower acylination of the other of R₇ and R₈ is R₁₀(O)CCH₂- or lower acylination of the other of R₇ and R₈ is R₁₀(O)CCH₂- or lower acylination of the other of R₇ and R₈ is R₁₀(O)CCH₂- or lower acylination of the other of R₇ and R₈ is R₁₀(O)CCH₂- or lower acylination of the other of R₇ and R₈ is R₁₀(O)CCH₂- or lower acylination of the other of R₁₀ and R₁₀ and R₁₀ and R₁₀ and R₁₀ are the other of R₁₀ and R₁₀ and R₁₀ and R₁₀ are the other of R₁₀ and R₁₀ and R₁₀ and R₁₀ are the other of R₁₀ and R₁₀ and R₁₀ are the other other of R₁₀ and R₁₀ are the other of R₁₀

 R_9 is hydrogen, optionally substituted lower alkyl, lower acyl or $R_{10}(O)CCH_{2^-}$;

R₁₀ is hydrogen, optionally substituted lower alkyl, alkoxy or hydroxy;

500 j

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m is 0, 1, 2 or 3;

 X_{t} and X_{t} are independently side that the from x_{t} anden, in the $ne^{R} t$ aubstrials taubsnuted hateroaryl loctionally substituted trearparettyl or hydroxyaligh, or p is 1 or 2. Y, and X₂ taren regetion form exec

> a pharmaceutically acceptable salt thereof, an N-oxide thereof a hydrate thereof or a solvate thereof.

X₃4s ay 4rcgen, hydrany, optionally substituted acryl, opnorally substituted him. **2. Of** The compound of claim 1 wherein Rais optionally substituted phenyl, is uno optionally substituted naphthyla optionally substituted thie nylior optionally substituted benzothienyl. 4 to 7 membered ring:

To all and mail is the compound of claims to wherein not is it nand mails it are the second of the

- The compound of claim 1 wherein X_2 and X_2 taken together are oxo. 4.
 - X_{ε} at $\mathcal{C}[X_{\varepsilon}]$ are hydrogen or taken together are ε NR ε The compound of claim 1 wherein X_1 , X_2 , X_3 and X_4 are hydrogen.
- - 7. The compound of claim 1 wherein X_5 and X_5 taken together are =NR5 wherein R5 is R6O2C-.

 X_{i} and X_{j} are incorporable by diagen, $R_{j}E_{k}Y_{j}$ $R_{j}C_{j}$ in $R_{i}V(O_{j})$ in $\Gamma_{i}V(A_{i})$ Faco-, iralo, evano, C.S

25 8. The compound of claim 1 wherein wherein substituted with X₅, X₅ and HR₂N- is attached to the 3-position of the phenyl.

hydrogen ut op filmally sinch ubid lower bill, in 1) and R_s are indeq The compound of claim 1 wherein at and facilities of is of the formula....

His ny tangan, mamaly subsit ër. 30

- 10. The compound of claim 1 wherein X_1 is hydrogen and X_2 , is carboxyalkyl, alkoxycarbonylalkyl or aryl, or X_1 and X_2 taken together form exo.
- 5 11. The compound of claim 1 wherein R_1 is R_3SO_2 .
 - 12. The compound of claim 1 wherein R₁ is R₃R₄NSO₂-.
 - 13. The compound of claim 1 wherein one of X_6 and $X_{6'}$ is amino in a para

 X_5 X_5 NHR₂

10 position relative to the

25

the fact of the section of the

- 14. A compound according to claim 1 which is
- Naphthalene-2-sulfonic acid {1-[3-(aminolminomethyl)benzyl]-2-oxopyrrolidin-3-(S)-yl)amide trifluoroacetate;

Dibenzofuran-2-sulfonic acid {1-[3-(aminoiminomethyl)benzyl]-5-oxopyrrolidin-3-yl}amide trifluoroacetate;

- Toluene-4-sulfonic acid (1-[3-(aminoiminomethyl)benzyl]-2-oxopyrrolidin-3-(S)-yl}amide trifluoroacetate;
 - 3,4-Dihydro-1H-isoquinoline-2-sulfonic acid (1-[3-(aminoiminomethyl)benzyl]-2-oxopyrrolidin-3-(S)-yl}amide trifluoroacetate;

3'-Methoxy-biphenyl-4-sulfonic acid (1-[3-(aminoiminomethyl)benzyl]-2-oxopyrrolidin-3-(S)-yl}amide trifluoroacetate;

Naphthalene-1-sulfonic acid [1-[3-(aminoiminomethyl)benzyl]-2-oxopyrrolidin-30 3-(S)-yl)amide trifluoroacetate;

5-Pyrid-2-ylthiophene-2-sulfonic acid (1-[3-(aminoiminomethyl)benzyl]-2-oxopyrrolidin-3-(S)-yl)amide trifluoroacetate;

	(S)-yl)amide-trifluoroacetate; eraction alexandrian area contention and the serious areas and the serious areas are serious areas and the serious areas are serious areas are serious areas are serious areas are serious areas areas areas are serious areas area
CALL TILL	can be verigh, alkopion about misyl or aryther 4, but 1 X, linear trigglish in
	7-Methoxynaphthalene-2-sulfonic acid {1-[3-(aminoiminomethyl)benzyl]-2-
5	oxopyrrolidin-3-(S)-yl}amide trifluoroacetatê; o lengograma < 17
	7-Ethoxynaphthalene-2-sulfonic acid {1-[3-(aminoiminomethyl)benzyl]-2-oxopyrrolidin-3-(S)-yl}amide trifluoroacetate;
10	. ເກີເຫລ ຄ່ວຽຽ ບກອນ X ໂດຍກົບ ກອງ ອາຍາກ ກໍາຄືກັນ ເຕືອນຕາດວັດຄືນີ້ ຂໍ້. 5-Chloro-6-methoxynaphthalene-2-sulfonic acid {1-[3-
	(aminoiminomethyl)benzyl]-2-oxopyrrolidin-3-(S)-yl}amide trifluoroacetate;
	ুভিত্তি হ ^{ান্ত্ৰি} কেন্ত্ৰ ভাৰতি কৰিছে এই ডিল্লাল এই ডিল্লাল
	(aminoiminomethyl)benzyli-2-oxopyrrolidin-3-(S)-yl}amide trifluoroacetate;
15	The hourist of the second of t
	7-Aminonaphthalene-2-sulfonic acid {1-[3-(aminoiminomethyl)benzyl]-2-
	oxopyrrolidin-3-(S)-yl)amide bistrifluoroacetate;
	•
30 <u>2</u> 0 3	Naphthalene-2-sulfonic acid (1-[4-(aminoiminomethyl)benzyl]-2-oxopyrrolidin
20	3-(S)-yl)amide trifluoroacetate;
	7-Methoxynaphthalene-2-sulfonic acid [1-(3-aminomethylbenzyl)-2-
£	oxopyrrolidin-3-(S)-yl]amide trifluoroacetate:
•	(S) All surgidity to the constitution of the control of the contro
. 25	Naphthalene-2-sylfonic acid (1-[3-(aminoiminomethyl)benzyl]-2-oxopyrrolidin-
2000	3-(S)-yl)methyl amide trifluoroacetate;
	And the state of t
	Naphthalene-2-sulfonic acid (1-[3-(aminoiminomethyl)benzyl]pyrrolidin-3-(S)-
	yl]amide bistrifluoroacetate;
30	
,	7-Methoxynaphthalene-2-sulfonic acid {1-[3-(aminoiminomethyl)benzyl]-2,5-
	7-Methoxynaphthalene-2-sulfonic acid {1-[3-(aminoiminomethyl)benzyl]-2,5- dioxopyrrolidin-3-(S)-yl}amide trifluoroacetate;
35	Naphthalene-2-sulfonic acid {1-[3-(aminoiminomethyl)benzyl]-2-oxopiperidin-3-yl)amide trifluoroacetate;
-	3-yijamide tilildoroacetate;

the and a substitution of

- 7-Methoxynaphthalene-2-sulfonic acid {1-[3-(amlnoimlnomethyl)benzyl]-2-oxoazepan-3-(S)-yl}amide trifluoroacetate;
- 7-Methoxynaphthalene-2-sulfonic acid {1-[3-(aminoiminomethyl)benzyl]-2-5 oxopyrrolidin-3-(S)-yl}methyl amide trifluoroacetate;
 - 6-Methoxynaphthalene-2-sulfonic acid {1-[3-(aminoiminomethyl)benzyl]-2oxopyrrolidin-3-(S)-yl]amide trifluoroacetate:
- 6-Methoxynaphthalene-2-sulfonic acid {1-[3-(aminoiminomethyl)benzyl]-2-10 oxopyrrolidin-3-(S)-yl}methyl amide trifluoroacetate: (Street and Authority of the Control
 - 2-[{1-[3-(Aminoiminomethyl)benzyl]-2-oxopyrrolidin-3-(S)-yl}-6methoxynaphthalene-2-sulfonylamino]-N-phenethylacetamide triffuoroacetate: (efstedeone and estamplify-(FI)-Extra Concord
 - 9,10-Dioxo-8a,9,10,10a-tetrahydroanthracene-2-sulfonic acid {1-[3-(aminoiminomethyl)benzyl]-2-oxopyrrolidin-3-(S)-yl}amide trifluoroacetate: E WARRY CONTRACTOR OF BURNESS
- 8-Chloro-7-methoxynaphthalene-2-sulfonic acid {1-[3-(aminoiminomethyl)-20 benzyl]-2-oxopyrrolidin-3-(S)-yl}amide trifluoroacetate:
- 7-Methoxynaphthalene-2-sulfonic acid {1-[4-(aminoiminomethyl)benzyl]-2oxopyrrolidin-3-(S)-yl}amide trifluoroacetate: Visit in the lumber of the land artific inno international problem of (8)-8 international (1972 and 1974) united in the second state of the second state of the second second

PROPERTORING THE REPORT OF THE REPORT OF THE PARTY OF THE

- 25 6,7-Dimethoxynaphthalene-2-sulfonic acid {1-[3-(aminoiminomethyl)benzyl]-2oxopyrrolidin-3-(S)-yl)amide trifluoroacetate: tentro antroction benefit (3-axopyroidin-3-(S)-yhrannyl amde
- Naphtho(2,3-d)-(1,3)dioxole-6-sulfonic acid {1-[3-(aminoiminomethyl)benzyl]-2-oxopyrrolidin-3-(\$)-vl}amide trifluoroacetate: 2019 (suppressed to the second second control of the composition of the control o
 - 7-Benzyloxynaphthalene-2-sulfonic acid (1-[3-(aminoiminomethyl)benzyl]-2oxopyrrolidin-3-(S)-yl}amide trifluoroacetate; 2 illumedity itemonimieninal (4-(3-(arineimienal) piete i seetadity itemonimienal) 2

responded the ACO will print in an expension tribuscased with

7-Hydroxynaphthalene-2-sulfonic acid (1-[3-(aminoiminomethyl)benzyl]-2oxopyrrolidin-3-(S)-yl}amide trifluoroacetate:

AMother - recittification - subjects acid (1-(3-(animoniary methylaber out it

: ;

- - S (hloro-3-methylbenzo[b]thiophene-2-sulfonic acid (1-[3-γxc#elVe-1 5 (aminoiminomethyl)benzy[]-2-οχοργιτοlidin-3-(S)-yl}amide trifluoroacetate;
 - (aminoiminomethyl)benzyl]-2-oxopyrrolidin-3-(S)-yl)methyl amide activitifuoroacetate;
 - 10 youngd(tyd)emphinionime)-E}-15 bios pinolius-S-ene wildconyouteM-6
 7-Methylnaphthalene-2-sulfonic;acid;{1-[3-(aminoiminomethyl)benzyl]-2oxopyrrolidin-3-(S)-yl}amide trifluoroacetate;
- -8-((y-(8))-1-dibilomydoxe-2-fiyznad(lydlerbonichonichA)-81-()]-2-31-(ethylnaphthalene-2-sulfonic acid (1,13-(aminoiminomethyl)benzyl]-2-31-(aminoiminometh
 - ்து-1) bios binoilus-S-e rependina orby de 15-1-01-01 இ. இ-மைப்-பா ந்து 5-Chloro-6-aminonaphthalene-2-sulfonic; acid {1-[3-ரி-மைப்பிட்ட கூட் (aminoimino methyl) benzyl]-2-oxopyrrolidin-3-(S)-yl] amide bistrifluoro acetate;
 - - 2-Methyl-1,2,3,4-tetrahydroisoguinolinyl-7-sulfonic acid: {1:[3-onyqoxc-(aminoiminomethyl)benzyl]-2-oxopyrrolidin-3-(S)-yl}amide bistrifluoroacetate;
- 2.5 n. ottychamonimionime i-8]-1) bioe nabilius-9-enaledinc aryxodiamiO-7.8 of 1.2,3,4-Tetrahydroisoquinolinyl-7-sulfonic_acid_{1,1,3,4-Tetrahydroisoquinolinyl-7-sulfonic_acid_{1,1,3,5-E-moilonymox.}

 (aminoiminomethyl)benzyl-2-oxopyrrolidin-3-(S)-yl)methyl amide

 (b) 4 (1.3) 4 (1.3) 4 (1.3) 4 (1.3) 5 (1.3) 6
 - 30 7-Methoxynaphthalene-2-sulfonic acid {1-[3-(aminoiminomethyl)benzyl]-2oxopyrrolidin-3-(S)-yl}-(4-nitrobenzyl)amide trifluoroacetate;
 - 7-Methoxynaphthalene-2-sulfonic acid (1-[3-(aminoiminomethyl)benzyl]-2οχοργιτο[idin-3-(S)-yl]-(4-aminobenzyl)amide bistrifluoroacetate; γείστ
 - elsiasnorealfin ebinat[ly-(ᢒ)-elsiatorydoxo // 7-Methoxynaphthalene-2-sulfonic acid {1-[3-(aminoiminomethyl)benzyl]-2oxopyrrolidin-3-(S)-yl}(3-nitrobenzyl)amid trifluoroacetate;

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- 10000 7-Methoxynaphthalene-2-sulfonic acid {1-[3-(aminoiminomethyl)benzyl]-2oxopyrrolidin-3-(S)-yl}(3-aminobenzyl)amide bistrifluoroacetate; and the second of the other second control of and the 7-Methoxynaphthalene-2-sulfonic acid {1-[3-(aminoiminomethyl)benzyl]-2oxopyrrolidin-3-(S)-yl}-(2-nitrobenzyl)amide trifluoroacetate: , madically one can be a considered by 3-[2-Oxo-3(S)-(2-phenylethenesulfonylamino)pyrrolidin-1-ylmethyl]benzamidine trifluoroacetate: (10) It was after the in the same with \$100 for it find the his exception 3-[2-Oxo-3(S)-(2-phenylethanesulfonylamino)pyrrolidin-1-ylmethyl]benzamidine trifluoroacetate: Time many the consultance and 1404 mine and the many back the [lmino-(3-{3-[7-Methoxynaphthalene-2-sulfonyl)methylamino]-2-oxo-3(S)pyrrolidin-1-ylmethyl]phenyl)methyl]carbamic acid ethyl ester; President design of the second only and the second of the 3-[2-Oxo-3(S)-{2-(pyridin-4-ylamino)-ethanesulfonylamino}-pyrrolidin-1ylmethyl]-benzamidine bistrifluoroacetate: and exceedibation of the sension methods of this becomes in the content of 2'-Methoxybiphenyl-4-sulfonic acid {1-[3-(aminoiminomethyl)benzyl]-2oxopyrrolidin-3(S)-vI) amide trifluoroacetate: THE CONTRACTOR STORE STO 5,6,7,8-Tetrahydrophenanthrene-3-sulfonic acid (1-[3-(aminoiminomethyl)benzyl]-2-oxo-3(S)-pyrrolidin-3-yl}amide trifluoroacetate: 3-(1-13) for a remoment yr) bencyl-2-oxobyrotidia (13), 3-y), 4% Isoquinolinyi-5-sulfonic acid (1-[3-(aminoiminomethyl)benzyi]-2-oxo-3(S)pyrrolidin-3-yl)amide bistrifluoroacetate: cell 1.13-12 mission and usually benzyll-2-oxopy religio-3 of hyllnaunthels of usual 5-Chlorothiophene-2-sulfonic acid (1-[3-(aminoiminomethyl)benzyll-2-oxo-3(S)-pyrrolidin-3-yl}amide trifluoroacetate; E. (E. F. S. et a normal standing) beazylg-2-pagycolldes. S. Sher, beganner
- -35° 7-Methoxy-2-naphthalenesulfonic acid (1-[3-(aminoiminomethyl)benzyl]-2-oxo-3(S)-pyrrolidin-3-yl}ethylamide trifluoroacetate:

oxo-3(S)-pyrrolidin-3-yl)amide trifluoroacetate;

2,4-Diaminoquinazoline-6-sulfonic acid (1-(3-(aminoiminomethyl)benzyl]-2-

ट [[१५३: Aminognia methyribeazyl]-2-oxopymolidin-3-(८९ द्वा-७-

	7-Methoxy-2-napthalenesulfonic acid {1-[3-(aminoiminomethyl)benzyl]	2-oxo
-S. Dysi	, 3(S)-pyrrollidin-3-yl)(3-fluorobenzyl)amide trifluoroacetate; x ortiotis-7	
	okopyrrolicin-3-(S)-yl)(3-aminobenzyi)amide bistriffu proapetate;	
	7-Methoxy-2-napthalenesulfonic acid {1-[3-(aminoiminomethyl)benzyl]-	2-oxo
5.5.5 5.7.5.5	[3(S)-pyrrolidin-3-yl)(4-methylbenzyl)amide trifluoroacetate;xodleM-T	Ċ.
	rxcpyn-sildio-5-(S)-yl)-(2-nitrobenzyl)amide trifluoroacetare;	
	7-Methoxy-2-napthalenesulfonic acid {1-[3-(aminoiminomethyl)benzyl]-	2-oxo-
	3(S),-pyrrolidin-3-yl}(3-methylbenzyl)amide trifluoroacetate;	
	benzamidine Irifluoroa (etata)	
10	7-Methoxy-2-napthalenesulfonic acid {1-[3-(aminoiminomethyl)benzyl]-	2-oxo-
	3(S)-pyrrolidin-3-yl)napthalene-2-ylmethylamide trifluoroacetate; SI-E	
	benzamidine trifluoroacetete;	
	7-Methoxy-2-napthalenesulfonic acid {1-[3-(aminoiminomethyl)benzyl]-	2-охо-
. (ප)-	3(S)-pyrrolldin-3-yl)(3-phenylallyl)amide-trifluoroacetate;-8)-6)-orimi)	
15	pyrrolidin-1-ylmethyi]phenyi)methyi carbamic acid othyl iister;	$\dot{\epsilon}$
	7-Methoxy-2-napthalenesulfonic acid {1-[3-(aminoiminomethyl)benzyl]-	2-oxo-
	3(S)-pyrrolidin-3-yl)(3-methylbenzyl)amide trifluoroacetate;	
	yar-athyllyt przamidine bistrilluorosostater	
	7-Methoxy-2-napthalenesulfonic acid {1-[3-(aminoiminomethyl)benzyl]-	2-охо-
20	3(S)-pyrrolidin-3-yl}(2-fluorobenzyl)amide, trifluoroacetate;	0S
	ക coyreddin-3(ട) ഗു amide triBuoreacetate;	
	2-Fluorobiphenyl-4-sulfonic acid {1-[3-(aminoiminomethyl)benzyl]-2-oxo)-3(S)-
	pyrrolidin-3-yl}methylamide,triffluoroacetate; heneriqostyrienie in 8 1,0,6	
· <u>14</u> 19.5	(aninolminomethyl)cenzyl]-2-oxo-3(5)-pyrrolidin-3-yi)amido trilluoro:	•
	3-[{1-[3-(Aminoiminomethyl)benzyl]-2-oxopyrrolidin-3(S)-3-yl}-(7-	214
- Cit	methoxynaphthalene-2-sulfonyl)amino]propionamide trifluoroacetate;	
	pytrolidin-3-yi)amide bistrifluordacetate;	
	2-[{1-[3-(Aminoiminomethyl)benzyl]-2-oxopyrrolidin-3-(S)-yl}naphthalen	e-2-
	sulfonylamino]-N-phenethylacejamide, trifluoroacetate;, no sidio cello-e	
30	3(S)-pyrrolistic 3-yillamide trifluoroacetare;	30
	2-[{1-[3-(Aminoiminomethyl)benzyl]-2-oxopyrrolidin-3-(S)-yl}biphenyl-4-	
St. Hart	sulfonylamino]-N-phenethylacetamide.trifluoroacetate;	
	assisted to the second of the	
	2-[{1-[3-(Aminoiminomethyl)benzyl]-2-oxopyrrolidin-3-(S)-yl]-7-	
ુ- છે; ≥વ\્ ડે- છે; ≥વ\્	methoxynaphthalene-2-sulfonylamino]-N-phenethylacetamide trifluoroac	cetate;
	3(S)-purolime 3-yllothylomide frilliomagnista:	

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. .

2-[{1-[3-(Aminoiminomethyl)benzyl]-2-oxopyrrolidin-3-(S)-yl}-7-methoxynaphthalene-2-sulfonylamino]-N-ethylacetamide trifluoroacetate;
The state of the s
2-[{1-[3-(Aminoiminomethyl)benzyl]-2-oxopyrrolidin-3-(S)-yl}-7-
methoxynaphthalene-2-sulfonylamino]-N,N-dimethylacetamide trifluoroacetate;
The state of the s

2-[{1-[3-(Aminoiminomethyl)benzyl]-2-oxopyrrolidin-3-(S)-yl}-7-methoxynaphthalene-2-sulfonylamino]-N-benzylacetamide trifluoroacetate;

2-[{1-[3-(Aminoiminomethyl)benzyl]-2-oxopyrrolidin-3-(S)-yl}-7-methoxynaphthalene-2-sulfonylamino]-N-(2-p-toluylethyl)acetamide trifluoroacetate;

2-[{1-[3-(Aminoiminomethyl)benzyl]-2-oxopyrrolidin-3-(S)-yl}-7- we methoxynaphthalene-2-sulfonylamino]-N-(4-methylbenzyl)acetamide

2-[{1-[3-(Aminoiminomethyl)benzyl]-2-oxopyrrolidin-3-(S)-yl}-7methoxynaphthalene-2-sulfonylamino]-N-[2-(3-fluorophenyl)ethyl]acetamide
trifluoroacetate; :stateneo.outhu somaffy-(3)2-n otto-2-jlysnen

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4,5-Dichlorothiophene-2-sulfonic acid {1-[3-(aminoiminomethyl)benzyl]-2-oxo-3(S)-pyrrolidin-3-yl}amide trifluoroacetate

35 ປະຊາຊະ າຍສ(lydternon.monthes: ປ້າ ປະໄທລະ ລະກວໄປເຂອກະຊະເປັດລຸກ-S-γະເວຕີສNi-V ເວີຍ 4,5-Dichlorothiophene -2-sulfonic acid (1-[3-(aminoiminomethyl)benzyl]-2-oxo-3(S)-pyrrolidin-3-yl}-methylamide trifluoroacetate;

	2-11-12 (Asimon anomal VI)bana, IJ-2 except rollalin-3-(S)-41-7-	
٠.,	-4,5-Dichlorothiophene-2-sulfonic acid [1-[3-(aminoiminomethyl)benzyl]	-2-oxo-
	3(S)-pyrrolidin-3-yl}benzylamide trifluoroacetate;	
	2-I(i-(3-(Aminoration) tehyl)benzyl)-2-exopyrrolidin-3-(S)-yl}-7-	
18 -5 01	c7-Methoxy-2-napthalenesulfonic acid (1-[3-(aminoiminomethyl)benzyl]-	2-oxo-
	3(S)-pyrrolidin-3-yl}-2-cyclopropylphenethylamide trifluoroacetate;	
	2-((1-(3 (Aminotinethmethyl)benzyl)-2-oxopyrrolidin-3-(S)-y.)-7-	
emic	3'-Methyl-biphenyl-4-sulfonic acid {1-[3-(aminoiminomethyl)benzyl]-2-	
	oxopyrrolidin-3(S)-yl} amide trifluoroacetate;	
10	z-{{1-i3-(Aminoim.: emethyi)ber-zyl}-2-adopymalidin-0-(S)-y:1-7-	24
	3-[{1-[3-(Aminoiminomethyl)benzyl]-2-oxopyrrolidin-3(S)-3-yl}-(7-rem	
	methoxynaphthalene-2-sulfonyl)amino]acetamide trifluoroacetate;	
	3-[{1-[3-(Aminoiminomethy!)benzyl]-2-oxopyrrolidin-3(S)-3-ŷl}-(7-1)]-S	
15	methoxynaphthalene-2-sulfonyl)amino]-2-methylacetamide trifluoroacet	ate;
	เตโนอาลอเลาสา	
	7-Methoxynaphthalene-2-sulfonic acid {1-[3-(aminoiminomethyl)benzyl]	-2-oxo-
	azetidin-3(S)-yi}amide:trifluoroacetate;sd/ly//te/mor/mic/nimA)-81-11j-2	
	chicxynepotinace io-2-sulfonylamino]-N-fa-methylbenzyljacetamloc	
20	7-Methoxynaphthalene-2-sulfonic acid {1-[3-(aminoiminomethyl)benzyl]	-2-ôxo-
	azetidin-3(S)-yl}benzylamide trifluoroacetate;	
	2-([1-[3-(/\min.coln.leamotaryljpaan.cylj-?-excpy.collaita-3-(S)-y/)-7-	
ະວາກຣະ	• • • •)-
	benzyl]-2-oxopyrrolidin-3(S)-yl]amide trifluoroacetate; (einseleoving t	
25		25
•	7-Methoxy-2-napthalenesultonic_acidr(1-[3-(aminoiminomethyl)benzyl]-2	:-oxo-
or th	3(S)-pyrrolidin-3-yl)-(2-methoxybenzyl)amide trifluoroacetate; (2011-915	
00	7-Methoxy-2-napthalenesulfonic acid (1-[3-(aminoiminomethyl)benzyl]-2	
30 ₃₇₁₀	, 3(S)-pyrrolidin-3-yl}-(3-methoxybenzyl)amide, trifluoroacetate; (xori = -	2.5
	the faceback of the control of the c	
	7-Methoxy-2-napthalenesulfonic acid (1-[3-(aminoiminomethyl)benzyl]-2	:-0X0-
io Sal	(3(S)-pyrrolidin-3-yl}-(4-methoxybenzyl)amide_trifluoroacetate; doi:10-2-15-	
	e tobac company at object its Outside the con-	

7-Methoxy-2-napthalenesulfonic acid {1-[3-(aminoiminomethyl)benzyl]-2-oxo-

estataneouseffor obmistyriten. Ay a erbian could-

3(S)-pyrrolldin-3-yl}(pyridin-2-ylmethyl)amide trifluoroacetate; (1017)

30

)

- 7-Methoxy-2-napthalenesulfonic acid {1-[3-(aminoiminomethyl)benzyl]-2-oxo-3(S)-pyrrolidin-3-yll(pyridin-3-ylmethyl)amide trifluoroacetate;
- 7-Methoxy-2-napthalenesulfonic acid {1-[3-(aminoiminomethyl)benzyl]-2-oxo-5 3(S)-pyrrolidin-3-yl}(pyridin-4-ylmethyl)amide trifluoroacetate;
 - 7-Methoxy-2-napthalenesulfonic acid {1-[3-(aminoiminomethyl)benzyl]-2-oxo-3(S)-pyrrolidin-3-yl}-(1-benzyl-1H-imidazol-2-ylmethyl)amide trifluoroacetate;
- 10 (1-Methyl-1H-imidazol-2-yl)benzene-4-sulfonic acid (1-[3-(aminoiminomethyl)benzyl]-2-oxopyrrolidin-3(S)-yl)amide trifluoroacetate:
 - 7-Methoxy-2-napthalenesulfonic acid {1-[3-(aminoiminomethyl)benzyl]-2-oxo-3(S)-pyrrolidin-3-yl}-(3-hydroxybenzyl)amide trifluoroacetate;
 - 7-Methoxy-2-napthalenesulfonic acid {1-[3-(aminoiminomethyl)benzyl]-2-oxo-3(S)-pyrrolidin-3-yl)-(2-hydroxybenzyl)amide trifluoroacetate;
- 7-Methoxy-2-napthalenesulfonic acid (1-[3-(aminoiminomethŷl)benzyl]-2-oxo-20 3(S)-pyrrolidin-3-yl)(pyrazol-3-ylmethyl)amide trifluoroacetate;
 - Quinoline-6-sulfonic acid (1-[3-(aminolminomethyl)benzyl]-2-oxopyrrolidin-3-(S)-yl}amide trifluoroacetate; the mass memory of the subble mysser of S
- 25 4-Pyridin-4-ylbenzenevsülfonic acid (1-[3-(aminoiminomethyl)benzyl]-2-oxopyrrolidin-3(S)-yl}amide bistriflüöröacetate;
- 7-Methoxy-2-napthalenesúlfonic acid (1-[3-(amíñoimínomethyl)benzýl]-2-oxo-3(S)-pyrrolidin-3-yl)(thiophene-2-ylmethyl)amíde trifflűoroacetate;
- ு வ N-Methylpyrid-4-ylphenyl-4-sulfönic acid (1-[3-(aminoiminomethyl)benzyl]-2-35 oxopyrrolidin-3(S)-yl}amide triflüöröacetate; ரிகளின் வர்கள் வருக்க வருக்க

CC:

- 2-Methoxyquinoline-7-sulfonic acid (1-[3-(aminoiminomethyl)benzyl]-2oxopyrrolidin-3-(S)-yl]amide trifluoroacetate;rvq;{ly-0-nibilonyo-(8)8
- xn-2-flv24;(6;[Methoxypyridin-2-yl)benzene-4:sulfonic/acid/(14[3-2-yr)nfield-1 (aminoiminomethyl)benzyl]-2-oxopyrrolidin-3(S)-yl)amide bistrifluoroacetate;
- The horsey 4:(3-Chloropyridin-2-yloxy)benzene-4-sulfonic acid (1:13- vacatieM-7 ുട്ടിളാളറ്റ് (aminoiminomethyl)benzyl]-2-oxopyrrolidin-3(S)-yl}amide trifluoroacetate:
 - 10 4-(N-Oxidopyridin,3-yl)benzene-4-sulfonic acid:{1-[3-mi Hi-yrac/v-...(aminoiminomethyl)benzyl]-2-oxopyrrolidin-3(S)-yl}amide trifluoroacetate;
- -2xo-S-1/4-Phenoxybenzene-4-sulfonic acid, (1-[3-(aminoiminomethyl)benzyl]-2oxopyrrolidin-3(S)-yl); amide trifluoroacetate; ri-E)-/ly-E-ribilonva-(6): 15
- 7-Methoxy-2-napthalenesulfonic acid {1-[3-(aminoiminomethyl)benzyl]-2-oxo-3(S)-pyrrolidin-3-yl)(thiophen-3-ylmethyl)amide trifluoroacetate (4-(3))
- -cxc-S-II-6-Methoxynaphthalene-2-sulfonic acid-(1-[3-(methoxyaminoiminomethyl)benzyl]-2-oxopyrrolidin-3:(S)-yl)methylamide/trifluoroacetate;nyg-(8)8
 - 6-Methoxynaphthalene-2-sulfonic acid (11-[3-(cyanoaminoiminomethyl)benzyl]-2-oxopyrrolidin-3-(S)-yl)methylamide trifluoroacetate;:ilin_ebros(ly-(8)
 - 6-Methoxynaphthalene-2-sulfonic acid (1-[3-(hydroxyaminoiminomethyl)benzyl]-2-oxopyrrolidin-3-(S)-yl}-methylamide trifluoroacetate;201.30%
 - 4-Amino-3-[3-(S)-(7-methoxynaphthalene-2-sulfonylamino)-2-oxopyrrolidin-1yl-methyl]benzamidine;dihydrochloride; enerlqoid)sh, 2-mbilonyq-(2-d
 - 4-Amino-3-[3-(S)-(7-methoxynaphthalene-2-sulfonylmethylamino)-2-oxopyrrolidin-1-yl-methyl]benzamidinestrifluoroacetate; 15.-nibitorryopiik
 - N-(4-Carbamimidoyl-2-{3-[(7-methoxynaphthalene-2-sulfonyl)methylamino]-2oxopyrrolidin-1-(S)-ylmethyl)phenyl)acetamide trifluroacetate; onygerm

- 4-Amino-3-[3-(S)-(4-tert-butylbenzenesulfonylamino)-2-oxopyrrolidin-1-yl-methyl]benzamidine trifluoroacetate;
- 3-Amino-5-[3-(S)-(7-methoxynaphthalene-2-sulfonylamino)-2-oxopyrrolidin-1yl-methyl]benzamidine bistrifluoroacetate;
- {4-(Aminoiminomethyl)-2-[3-(7-methoxynaphthalene-2-sulfonylamino)-2-oxopyrrolidin-1-ylmethyl]phenoxy}acetic acid methyl ester trifluoroacetate;
- 10 {4-(Aminoiminomethyl)-2-[3-(7-methoxynaphthalene-2-sulfonylamino)-2-oxopyrrolidin-1-ylmethyl]phenoxy)acetic acid trifluoroacetate;
 - 2-Chloro-6-nltrophenoxybenzene sülfönic acid (1-[3-16-2]) (aminoiminomethyl)benzyl]-2-oxopýrrolidin-3(S)-yl}amide triffűörőacetate;
 - 4-[3-(S)-(7-Methoxynaphthalene-2-sulfonylamino)-2-oxopyrrolidin-1-ylmethyl]-thiophene-2-carboxamidine-trifluoroacetate;
- 4-{3-(S)-[(7-Methoxynaphthalene-2-sulfonyl)methylamino]-2-oxopyrrolidin-1-20 // ylmethyl}thiophene-2-carboxamidine trifluoroacetate;
 - 2-[[1-(5-Carbamimidoýlthiophene-3-ýlmethýl)-2-öxopyrrolidin-3-(S)-yl](7-methoxynaphthalene-2-sulfonyl)āminojācetamide triffuoroacetate;
- 25 4-{3-(S)-[(7-Methoxynaphthalene-2-sulfonyl)benzylaminoj-2-oxopyrrolidin-1-ylmethyl}thiophene-2-carboxámidine trifluoróacetate;
- - 5-{3-(S)-[(7-Méthöxyhäphthalené-2-sulfohyl)methylamino]-2-oxopyrrolidin-1-ylmethyl}thiophene-3-carboxamidîne trifluoroacetate;
- 4-{3-(S)-[(-5-Chloro-3-methylbehzo[b]thlophehe-2-sulfonyl)behzylamino]-2-35 oxopyrrolidin-1-ylmethyl)thlophehe-2-carboxamidine frifluoroacetate;

- ...4-{3-(S)-[(Methanesulfonyl)-(3-phenylpropyl)amino]-2-öxopyrrolidin-1ylmethyl}thiophene-2-carboxamidine_trifluoroacetate;nashed[[vdfs.co
- #5# τη 4-[3-(S)-[(Methanesulfonyl)(naphthalene-2-yl)amino]-2-οχοργιτοlidin-1-5 ylmethyl}thiophene-2-carboxamidinestrifluoroacetate; πασθίνησεσιον σ
 - S ...4-(3-(\$)-[(4,5-Dichlorothiophene-2-sulfonyl)benzylamino]-2-oxopyrrolidin-1-- - - ylmethyl}thiophene-2-carboxamidine trifluoroacetate;- t-nioriomyαν σ
- 10 4-{3-(\$)-[(5-Chloro-3-methylbenzo[b]thiophene-2-sulfonyl)methylamino]-2-oxopyrrolidin-1-ylmethyl)thiophene-2-carboxamidine trifluoroacetate;
- 2-[[1-(5-Carbamimidoy|thiophene-3-y|methyl)-2-oxopyrrolidin-3-(S)-yl]-(7-methoxynaphthajene-2-sulfonyl)amino]-N-phenethylacetamide trifluoroacetate;
- dichlorothiophene-2-sulfonyl)amino]-N-benzylacetamide-trifluoroacetate;
 - 2-[[1-(5-Carbamimidoylthiophene-3-ylmethyl)-2-oxopyrrolidin-3-(S)-yl]-(7-methoxynaphthalene-2-sulfonyl)amino]-N-benzylacetamide trifluoroacetate;
 - 2-[[1-(4-Garbamimidoylthiophene-2-ylmethyl)-2-oxopyrrolidin-3-(S)-yl]-(7-methoxynaphthalene-2-sulfonyl)amino]acetamide-trifluoroacetate;
 - 25. 2-[[1-(4-Carbamimidoylthiophene-2-ylmethyl)-2-oxopyrrolidin-3-(S)-yl]-(5-chloro-3-methylbenzo[b]thiophene-2-sulfonyl)amino]acetic acid methyl ester;
 - رِيْرِ عَلَيْهِ عَلَى الْمِرِيِّ عَلَيْهِ عَلَيْهِ عَلَيْهِ عَلَيْهِ عَلَيْهِ عَلَيْهِ عَلَيْهِ عَلَيْهِ عَلَي ylmethyl}thjophene-2-carboxamidine_bistrifluoroacetate: المَّالِيْهِ عَلَيْهِ عَل
 - 4-{3-(\$)-[(7-Aminonaphthalene-2-sulfonyl)methylamino]-2-oxopyrrolidin-1-ylmethyl}thiophene-2-carboxamidine;bistrifluoroacetate;
 - 2-[[1-(5-Carbamimidoy|thiophene-3-y|methyl)-2-oxopyrrolidin-3-(S)-yl]-(7-aminonaphthalene-2-sulfonyl)aminolacetamide bistrifluoroacetate:

25

- 4-[3-(S)-(6-Amino-5-chloro-2-sulfonylamino)-2-oxopyrrolidin-1-ylmethyl]-thlophene-2-carboxamidine trifluoroacetate;
- 4-{3-(S)-[(6-Amino-5-chloro-naphthalene-2-sulfonyl)methylamino]-2-oxopyrrolidin-1-ylmethyl}thiophene-2-carboxamidine trifluoroacetate;
 - 2-[[1-(5-CarbamimidoyIthiophene-3-ylmethyl)-2-oxopyrrolidin-3-(S)-yl]-(6-amino-5-chloronaphthalene-2-sulfonyl)amino]acetamide trifluoroacetate;
- 4-[3-(S)-(6-Aminonaphthalene-2-sulfonylamino)-2-oxopyrrolldin-1-ylmethyl]-thiophene-2-carboxamidine dihydrochloride;
 - 5-[3-(S)-(7-Methoxynaphthalene-2-sulfonylamino)-2-oxopyrrolidin-1-ylmethyl]-thiophene-2-carboxamidine trifluoroacetate;
 - 5-{3-(S)-[(7-Methoxynaphthalene-2-sulfonyl)methylamino]-2-oxopyrrolidin-1-ylmethyl}thiophene-2-carboxàmidine trifluoroacetate;
- 5-{3-(S)-{(7-Methoxynaphthalene-2-sulfonyl)benzylamino}-2-oxopyrrolidin-1-20 ylmethyl}thiophene-2-carboxamidine trifluoroacetate;

and content of the California of the

- [Amino-(4-{3-(S)-(7-methoxynaphthalene-2-sulfonyl)methylamino]-2access oxopyrrolidin-1-ylmethyl}thiophene-2-yl)methylenejcarbamic acid methyl ester trifluoroacetate;
 - 4-{3-(S)-[(7-Methoxynaphthalene-2-sulfonyl)methylamino]-2-oxopyrrolidin-1-ylmethyl}thiophene-2-N-hydroxycarboxamidine trifluoroacetate;
- 4-[3-(S)-(7-Methoxynaphthalene-2-sulfonylamino)-2-oxopyrrolidin-1-ylmethyl]30 pyridine-2-carboxamidine trifluoroacetate;
 - 4-{3-(S)-[(7-Methoxyñaphthálene-2-sulfoñyl)benzylamino]-2-oxopyrrolidin-1-ylmethyl)pyridine-2-carboxamidine trifluoroacetate;
- 35 4-{3-(\$)-[(7-Methoxynaphthalene-2-sulfonyl)methylamino]-2-oxopyrrolidin-1-ylmethyl)pyridine-2-carboxamidine trifluoroacetate;

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āvr	4-[3-(\$)-(5-Chloro-3-methylbenzo[b]thiophene-2-sulfonylaminó)-2 oxopyrrolidin-1-ylmethyl]pyrldine-2-carboxamidine-trifluoroacetate;
5	4-{3-(S)-[(5-Chloro-3-methylbenzo[b]thiophene-2-sulfonyl)methylamino]-2-oxopyrrolidin-1-ylmethyl)pyridine-2-carboxamidine-trifluoroacetate;
), 51	2-{[1-(2-Carbamimidoylpyridine-4-ylmethyl)-2-oxopyrrolidin-3-(S)-yl]-(7-methoxynaphthalene-2-sulfonyl)amino}acetamide trifluoroacetate;
10 (rvrila	2-{[1-(2-Carbamimidoyl-pyridine-4-ylmethyl)-2-oxopyrrolidin-3-(S)-fyl]-(7-(-) methoxynaphthalene-2-sulfonyl)amino}-N-phenethylacetamide rigordi trifluoroacetate;
-{ vrt am 15	4-{3-(S)-[(7-Methoxynaphthalene-2-carboxamidine trifluoroacetate;
1.591.	4-{3-(S)-[(7-Methoxynaphthalene-2-sulfonyl)thiophen-3-ylmethylamino]-2-oxopyrrolidin-1-ylmethyl}thiophene-2-carboxamidine trifluoroacetate;
20 "	ijonyczn. o.3. zr.imgiyknedflynatius-StansfortidgscyxotteM-7)]-(Elt-6)-: 4-{3-(S)-[(4-(6-Nitro-2-chlorophenoxy)benzenesulfonyl)amino]-2-oxopyrrolidin- 1-ylmethyl}thiophene-2-carboxamidine trifluoroacetate;
945W	5-{3-(S)-[(7-Methoxynaphthalene-2-sulfonylamino]-2-oxopyrrolidin-1-ylmethyl)-furan-2-carboxamidine trifluoroacetate; and
∠5 ··· 1,"	4-[3-(\$)-(5-Chloro-3-methylbenzo[b]thiophene-2-sulfonylamino)-2

15. A compound according to claim 14 which is according to claim 30 to blind the control of the property of th

7-Methoxynaphthalene-2-sulfonic acid {1-[3-(aminoiminomethyl)benzyl]-2-oxopyrrolidin-3-(S)-yl)methyl amide trifluoroacetate. Only (€ € €) ⊕

16. A compound according to claim 14 which is

3'-Methoxy-biphenyl-4-sulfonic acid (1-[3-(aminoiminomethyl)benzyl]-2-v oxopyrrolidin-3-(S)-yl}amide trifluoroacetate.

47. J. 5. 5

A compound according to claim 14 which is The second of the September of e o type or a light of many

5-Pyrid-2-ylthiophene-2-sulfonic acid {1-[3-(aminoiminomethyl)benzyl]-2oxopyrrolldin-3-(S)-yl}amide trifluoroacetate. 5

A compound according to claim 14 which is on this and twenton in his his big blur and the

Transfer in Maria

7-Methoxynaphthalene-2-sulfonic acid {1-[3-(aminoiminomethyl)benzyl]-2oxopyrrolidin-3-(S)-yl}amide trifluoroacetate. 10 MORNEY MENO TO CONDICORE LINE OF MELL

A compound according to claim 14 which is

7-Aminonaphthalene-2-sulfonic acid {1-[3-(aminoiminomethyl)benzyl]-2-15 oxopyrrolidin-3-(S)-yl}amide bistrifluoroacetate. Our seeds according to

A compound according to claim 14 which is 20. A Service that is according to the following property of the constitution of

The first to the first of

5-Chloro-3-methylbenzo[b]thiophene-2-sulfonic acid {1-[3-

- (aminoiminomethyl)benzyl]-2-oxopyrrolidin-3-(S)-yl]amide trifluoroacetate. 20 ive brimish it ambrevous in regime the
 - A compound according to claim 14 which is Canolics resultant acid (1-[3-(aminormounistry))beary[]-k-oxopyn-

2-[{1-[3-(Aminoiminomethyl)benzyl]-2-oxopyrrolidin-3-(S)-yl}-7-

- methoxynaphthalene-2-sulfonylamino]-N-phenethylacetamide trifluoroacetate. 25 A compound assembly to slaim 14 which is
- A compound according to claim 14 which is 4 Amil. (243 (S), (7-metholographthalene-2-si conglamino 43-exist you turn of

2-[{1-[3-(Aminoiminomethyl)benzyl]-2-oxopyrrolldin-3-(S)-yl}-7-

30 methoxynaphthalene-2-sulfonylamino]-N-benzylacetamide trifluoroacetate.

A consuland accommend of aim 14 ways a

A compound according to claim 14 which is 23. #-Amino-200 Sper7-mula Lynaphthalene 2-outly byt-mempeaming)-2

2-[{1-[3-(Aminoiminomethyl)benzyl]-2-oxopyrrolldin-3-(S)-yl}-7-

methoxynaphthalene-2-sulfonylamino]-N-(2-pyridin-3-yl-ethyl)acetamide 35 bistrifluoroacetate.

23	256

	24.	A compound according to claim 14 which is	
3-,0		s. declarationals of gnibropae honocomes A 5.1. Dichlorothiophene-2-sulfonic acid {1-[3-(aminoiminomethyl)benzyl -pyrrolidin-3-yl)amide trifluoroacetates-S-energoidiy-s-biry-5-8]-2-oxo-
5	25.	oxope trolidin-3-(8)-yl}amide trlfluoroabatate. si holdward with the mission of the state of the	5
1-Carro	M-'E	ethyl-biphenyl-4-sulfonic acid {1-[3-(aminoiminomethyl)benzyl]-2- pyrrolidin-3(\$)-yl} amide trifluoroacetate;	
10`	26.	experiod din-8-(3-yHamide uffilio-baceatata. A compound according to claim 14-which is	91
. <u>s</u> ." 15	3-[{1- meth 27.	et doidy &t crisio of gaibreose barroqued A01 -{3-(Aminoiminomethyl)benzyl]-2-oxopyrrolidin-3(S)-3-yl}-{7	čl
·	7-Me 3(S)-	A compound according to claim 14 which is a design 41 mistored performs a compound of the com	2-0x0- 0S
	Quino	A compound according to claim 14 which is all doldweet mistoral guildness bruckwas A 1.12 pline-6-sulfonic acid {1-[3-(aminoiminomethyl)benzyl]-2-oxopyrrolic plamide trifluoroacetate. Sulvaned(lydismonlinic plants) 12-13-13-13-13-13-13-13-13-13-13-13-13-13-	
.atai -25 .atai -3 o	ເວນໄດ້: 29.	methoxymar principles 3. autonylamino)-N-phene phacetern (c.) A compound according to claim 14 which is	25.
20	yl-me	22. A comportation of pribrocos are composited in the internal A composite internal A composi	idin-1-
30	30.	The abinuteralyzned-vi-[orangiyacitus S-eneralitique vy.odem A compound according to claim 14 which is	75
		endows 61 misso of pribrophs brugering A	
9 0.1		methory yeaphthusin seryibenzymezkowi kyndin-3 ykonymethory opitaliany spennyme	38
		atole as a substitution of the substitution of	

38.

	31. A compound according	to claim 14 which is
:	in a like of the first	na na galanda Berlina nga na masa na ma
	4-Amino-3-[3-(S)-(4-tert-butylb	enzenesulfonylamino)-2-oxopyrrolidin-1-yl-
5	methyl]benzamidine trifluoroad	etate.
	32. A compound according	o claim 14 which is
		Republic antide terms of the feet of
	{4-(Aminoiminomethyl)-2-[3-(7-	methoxynaphthalene-2-sulfonylamino)-2-
10	oxopyrrolidin-1-ylmethyl]pheno:	y)acetic acid methyl ester trifluoroacetate.
	सं कार्यक्त असे ।	made on paradicine been green in the CA
	A compound according t	
		energer-donal Central Artist 13 (1997)
	4-[3-(S)-(7-Methoxynaphthalen	e-2-sulfonylamino)-2-oxopyrrolidin-1-ylmethyl]-
15	thiophene-2-carboxamidine triff	uoroacetate.
		mieto po godanskoe pod se nijelo ili 1919. 🤼 💮 🤼
	34. A compound according to	claim 14 which is
		galani series de Redicestados e dos series e
	4-{3-(S)-[(7-Methoxynaphthaler	e-2-sulfonyl)methylamino]-2-oxopyrrolidin-1-
20	ylmethyl}thiophene-2-carboxam	
		misto (in including strong and including
	A compound according to	
•		it ue-S-er - terttifgsnun,mA-11, (C)-P}-t
	2-[[1-(5-CarbamimidoyIthiopher	e-3-ylmethyl)-2-oxopŷrrolidin-3-(S)-yl](7-
25		amino]acetamide trifluoroacetate.
		43. A socipound according to claim
	A compound according to	
$\{n_i, \cdots$		8-3-(8.47 Mamos yright) alere-8-sul
		o[b]thiophene-2-sulfonylamino)-2-oxo-
30		2-carboxamidine trifluoroacetate.
		ee
	A compound according to	
• ;	• •	4-(3-11)457-Ited.oxynaphthalene-1-su
	4-{3-(S)-[(5-Chloro-3-methylber	zo[b]thiophène-2-sulfonyl)methylamino]-2-
35	oxopyrrolidin-1-ylmethyl}thiophe	ne-2-carboxamidine trifluoroacetate.
	te which is	45. Company of accurate to faint

A compound according to claim 14 which is

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	- Anno 6-43-43-43-43 dependent of the following of the first of the fi
√ .` 5	39. A compound according to:claim: 4 which is the image of divided to the
	ce. The composite according to claim 114 Which is
	[Amino-(4-{3-(S)-(7-methoxynaphthalene-2-sulfonyl)methylamino]-2-
	oxopyrrolidin-1-ylmethyl}thiophene-2-yl)methylene]carbamic acid methyl ester
Ž.	(chilluoroacetate, energy spacetory is a character of the spacetory in the control of the character of the c
10	oxcovere dead ylmetry lightenoxy) acid acid metry light trimercaces:
	40. A compound according to claim 14 which is
	32. A compound according to datin 14 which is
	4-{3-(S)-[(6-Amino-5-chloro-naphthalene-2-sulfonyl)methylamino]-2-
i alter	oxopyrrolidin-1-ylmethyl)thiophene-2-carboxamidine trifluoroacetate.
15	figure 15 this phene-2-parhoxam sine uffluerus retate.
	41. A compound according to claim 14 which is
	SA. A compound scoolang to claim 14 which is
	4-[3-(S)-(6-Amino-5-chloro-2-sulfonylamino)-2-oxopyrrolidin-1-ylmethyl]-
FARE	; thiophene-2-carboxamidine trifluoroacetate (signification of the winds of the win
20	the interpolation of the property of the prope
	42. A compound according to claim 14 which is
	e a sumbound advoruing to claim 14 which is
	4-{3-(S)-[(7-Aminonaphthalene-2-sulfonyl)benzylamino]-2-oxopyrrolidin-1-
	ylmethyl)thiophene-2-carboxamidine bistrifluoroacetate
25	in athory are thatene-2-sulfonyi) ameroja cetamida trifluoro scerate.
	43. A compound according to claim 14 which is
	96 Compound according to platm 14 which is
	4-[3-(S)-(7-Methoxynaphthalene-2-sulfonylamino)-2-oxopyrrolidin-1-ylmethyl]-
	pyridine-2-carboxamidine trifluoroacetate dyntem-8 4. 10 8-(8)-2-
30	10 cymerkun i yimethyuthiopher-2-carboxanidine trifluoroscotajos
	44. A compound according to claim 14 which is
	200 2 more and percepting to dains 14 which is
	4-{3-(S)-[(7-Methoxynaphthalene-2-sulfonyl)benzylamino]-2-oxopyrrolidin-1-
51	_ylmethyl}pyridine-2-carboxamidine, trifluoroacetate. ကစ်ကြေး) (၁)-(၁)-မျာ
35	The actual of the third history and the carbox and the confidence of the confidence
	45. A compound according to claim 14 which is
	appeal by bit minds as germonae his marries 🐧 💎 🤏

2-{[1-(2-Carbamimidoyl-pyridine-4-ylmethyl)-2-oxopyrrolidin-3-(S)-yl]-(7-methoxynaphthalene-2-sulfonyl)amino}-N-phenethylacetamide trifluoroacetate.

5 46. A compound according to claim 14 which is

4-{3-(S)-[(7-Methoxynaphthalene-2-sulfonyl)thiophen-3-ylmethylamino]-2-oxopyrrolidin-1-ylmethyl}thiophene-2-carboxamidine trifluoroacetate.

10 47. A compound according to claim 14 which is

4-{3-(\$)-[(4-(6-Nitro-2-chlorophenoxy)benzenesulfonyl)amino]-2-oxopyrrolidin-1-ylmethyl}thiophene-2-carboxamidine trifluoroacetate.

15 48. The compound according to claim 1 of the formula

wherein R is hydrogen, methyl, aralkyl, heteroaralkyl, HO₂CCH₂-, HOC(O)CH₂-, 20 H₂NC(O)CH₂-, (aralkyl)HNC(O)CH₂- or (heteroaralkyl)HNC(O)CH₂-; X₆ is hydrogen or amino; and R₁ is selected from the group of formulae

The converse of the months of the state of t A compound according to daim 14 water is

nepara http://ides-s.actor/indeapyxor<u>ina</u>4-7)(1-Majhoxagaaphilipagas-s.actor)

Alecticand according to days: 19 which is . 7 5

יוריקפה סריים והבי ובחל בל יוב כפוביי ביה ויום מרייקי כל לבהחם

49. The compound according to claim 1 of the formula

wherein R is hydrogen, methyl, aralkyl, heteroaralkyl, HO₂CCH₂-, HOC(O)CH₂-, H₂NC(O)CH₂-, (aralkyl)HNC(O)CH₂- or (heteroaralkyl)HNC(O)CH₂-; and R₁ is selected from the group of formulae

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15 50. A compound of the formula II

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wherein X₃, X₄ and m are as defined according to claim 1, P₁ is alkyl, aralkyl or aryl, and P₂ is (alkyl, aralkyl or aryl)carbamate.

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51. A compound of the formula

wherein Ar¹, R, X₁, X₂, X₂, X₃, X₄, X₅, x and n are as defined according to claim 1, and P₂ is (alkyl, aralkyl, or aryl)carbamate or R₁ as defined according to claim 1.

52. A compound of the formula X.

15

$$X_{1}$$

$$X_{1}$$

$$X_{1}$$

$$X_{1}$$

$$X_{2}$$

$$X_{2}$$

$$X_{2}$$

$$X_{6}$$

$$X_{6}$$

$$X_{6}$$

$$X_{6}$$

$$X_{1}$$

$$X_{2}$$

$$X_{2}$$

$$X_{3}$$

$$X_{4}$$

$$X_{2}$$

$$X_{2}$$

$$X_{2}$$

$$X_{3}$$

$$X_{4}$$

$$X_{5}$$

$$X_{2}$$

$$X_{6}$$

$$X_{6}$$

$$X_{6}$$

$$X_{6}$$

$$X_{6}$$

$$X_{6}$$

$$X_{6}$$

wherein Ar^1 , X_1 , X_2 , X_3 , X_4 , X_8 , X_8 , X_9 , m and n are as defined according to claim 1, and $P_{2^{-1}}$ is hydrogen or (alkyl, aralkyl or aryl)carbamate.

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36. A compound of the formula XII.

15

$$X_{1}$$

$$X_{1}$$

$$X_{1}$$

$$X_{1}$$

$$X_{1}$$

$$X_{2}$$

$$X_{2}$$

$$X_{1}$$

$$X_{2}$$

$$X_{2}$$

$$X_{3}$$

$$X_{2}$$

$$X_{2}$$

$$X_{3}$$

$$X_{4}$$

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$$X_{5}$$

$$X_{7}$$

$$X_{8}$$

$$X_{1}$$

$$X_{1}$$

$$X_{2}$$

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$$X_{5}$$

$$X_{7}$$

$$X_{8}$$

$$X_{1}$$

$$X_{1}$$

$$X_{2}$$

$$X_{3}$$

$$X_{4}$$

$$X_{2}$$

$$X_{3}$$

$$X_{4}$$

$$X_{5}$$

$$X_{5}$$

$$X_{7}$$

$$X_{8}$$

$$X_{8$$

- wherein X_1 , X_2 , X_3 , X_4 , X_6 , X_6 and m are as defined according to claim 1 and P_2 is (alkyl, aralkyl or aryl)carbamate.
 - 53. A pharmaceutical composition comprising the compound according to claim 1 and a pharmaceutically acceptable carrier.
 - 54. A method for treating a patient suffering from a physiological disorder capable of being modulated by inhibiting an activity of Factor Xa by administering a therapeutically effective amount of the compound according to claim 1.

55. The method according to claim 54 wherein the physiological disorder is venous vasculature, arterial vasculature, abnormal thrombus formation, acute myocardial infarction, unstable angina, thromboembolism, acute vessel closure associated with thrombolytic therapy, percutaneous transluminal coronary angioplasty, transient ischemic attacks, stroke, intermittent claudication or bypass grafting of the coronary or peripheral arteries, vessel luminal narrowing, maintenance of vascular access patency in long-term hemodialysis patients, pathologic thrombus formation occurring in the veins of the lower extremities following abdominal, knee and hip surgery, a risk of pulmonary

25 thromboembolism, or disseminated systemic intravascular coagulopathy occurring in vascular systems during septic shock, certain viral infections or cancer.

INTERNATIONAL SEARCH REPORT

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International application No. PCT/US96/09816

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	(Columbus, Ohio, USA), page 8	61, column 1, the abstract	
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INTERNATIONAL SEARCH REPORT

International application No. PCT/US96/09816

A. CLASSIFICATION OF SUBJECT MATTER: US CL:
540/606; 546/141, 223, 276.4; 548/527, 557; 514/212, 307, 309, 343, 329, 422, 426
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